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#6

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent 4,215,215

WERNER BOLLAG, RUDOLF RUEGG and GOTTLIEB RYSER

Attn: Box Patent Ext.

Issue Date: July 29, 1980

For: 9-PHENYL-NONATE TETRAENE COMPOUNDS

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156

Nutley, New Jersey 07110
November 7, 1986

Honorable Commissioner of Patents & Trademarks

Washington, D.C. 20231

S i r:

Pursuant to 35 USC 156, Hoffmann-La Roche Inc. ("Roche"), a corporation organized under the laws of the State of New Jersey and owner of captioned U.S. Patent No. 4,215,215 by assignments recorded on January 21, 1977 at reel 3377, frames 050-053, submits this application for extension of the term of said patent.

Applicant seeks extension of the term of U.S. Patent No. 4,215,215 for two (2) years, from July 29, 1997 to July 29, 1999, and provides the following information in accordance with 35 USC 156(d) and the initial Patent and Trademark Office

CERTIFICATE OF MAILING
By EXPRESS MAIL

Mailing Label Number B28074575

Date of Deposit Nov. 21, 1986

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1 10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Print Name Mark E. Waddell

Signature Mark E. Waddell

guidelines published October 9, 1984 at 1047 O.G. 17. The information follows the numerical format set forth in Section D(b) of the initial guidelines.

(1) A Complete Identification Of The Approved Product As By Appropriate Chemical And Generic Name, Physical Structure Or Characteristics

The approved product contains etretinate, the sole active ingredient of the drug Tegison® oral, the package insert for which is attached as Exhibit 1.

The term "approved product" is defined in 35 U.S.C. 156(a) as the "product" referred to in paragraphs (4) and (5) of subsection (a). In turn, the word "product" is defined in 35 U.S.C. 156(f)(1)(A) to comprise a "human drug product" which is prescribed in 35 U.S.C. 156(f)(2) to include "the active ingredient of a new drug . . . including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient." Accordingly, the approved product subject to this Application includes etretinate as well as its salts and esters, as a single ingredient or in combination with another active ingredient.

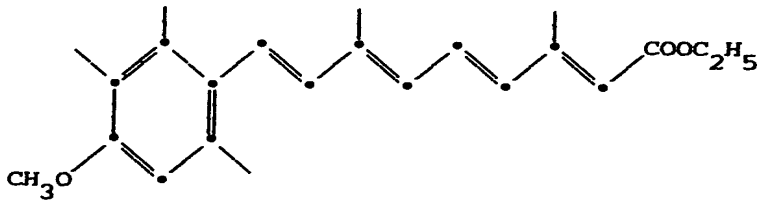
Etretinate has the following chemical names:

1) ethyl all trans-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraen-1-oic acid ethyl ester;

2) ethyl (all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-di-methyl-2,4,6,8-nonatetraenoate;

3) all trans-9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester.

Etretinate has the structural formula:



"Etretinate" is the non-proprietary name approved by the USAN council for the active ingredient of Tegison oral.

(2) A Complete Identification Of The Federal Statute Including The Applicable Provision Of Law Under Which The Regulatory Review Occurred

The regulatory review occurred under Sections 505 of the Federal Food, Drug and Cosmetic Act ("FD&C"), 21 USC 301 et seq.

(3) An Identification Of The Date On Which The Product Received Permission For Commercial Marketing Or Use Under The Provision Of Law Under Which The Applicable Regulatory Review Period Occurred

Tegison oral was approved by the Food and Drug Administration ("FDA") for commercial marketing or use under Section 505 of the FD&C on September 30, 1986.

(4) A Statement That The Application Is Being Submitted Within The Sixty Day Period Permitted For Submission And An Identification Of The Date Of The Last Day On Which The Application Could Be Submitted

This Application is being submitted within the permitted sixty day period, said period will expire on November 29, 1986.

(5) A Complete Identification Of The Patent For Which An Extension Is Being Sought By The Name Of The Inventor, The Patent Number, And The Date Of Issue

The complete identification of the patent for which an extension is being sought follows:

Inventors: Werner Bollag, Rudolf Ruegg, and Gottlieb Ryser

Patent No: 4,215,215

Issue Date: July 29, 1980

(6) A Copy Of The Patent For Which An Extension Is Being Sought, Including The Entire Specification (Including Claims) And Drawings, In The Form Of A Cut-Up Copy Of The Original Patent With Only A Single Column Of The Printed Patent Securely Mounted Or Reproduced In Permanent Form On One Side Of A Separate Paper

A copy of the patent in the requested form of a cut-up copy is attached as Exhibit 2.

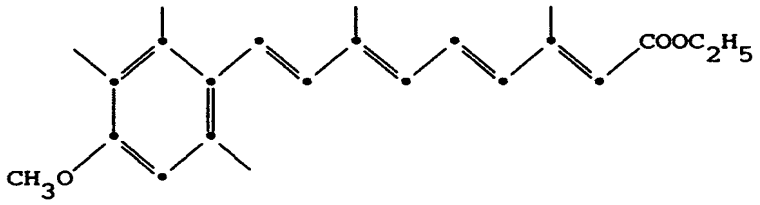
(7) A Copy Of Any Disclaimer, Certificate Of Correction, Receipt Of Maintenance Fee Payment, Or Reexamination Certificate Issued In The Patent

No disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate has been issued for U.S. Patent No. 4,215,215.

(8) A Statement That The Patent Claims The Approved Product Or A Method Of Using Or Manufacturing The Approved Product, And A Showing Which Lists Each Applicable Patent Claim And Demonstrates The Manner In Which Each Applicable Patent Claim Reads On The Approved Product Or A Method Of Using Or Manufacturing The Approved Product

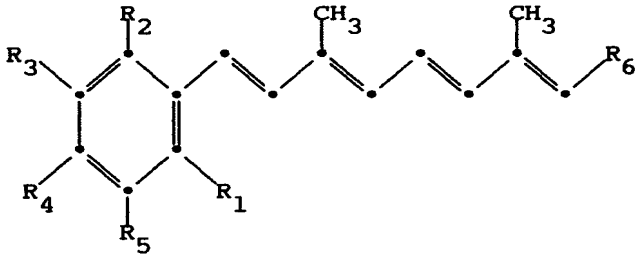
U.S. Patent No. 4,215,215 claims etretinate, its esters and pharmaceutically acceptable salts in claims 1, 2, 3 and 5.

Etretinate, the active ingredient of the approved product, has the chemical structure:



Claim 1, in an edited form, reads as follows:

1. A compound of the formula:

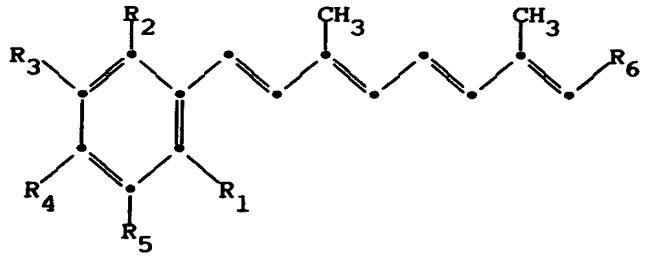


wherein R_1 and R_2 are lower alkyl; R_3 is . . . lower alkyl . . .; R_4 is lower alkoxy; R_5 is hydrogen . . .; and R_6 is . . . alkoxycarbonyl where its alkoxy moiety is unsubstituted . . ., or pharmaceutically acceptable salts thereof.

Etretinate has the chemical structure identified above. When in claim 1, R_1, R_2 and R_3 each are methyl, R_4 is methoxy and R_6 is alkoxycarbonyl and in particular R_6 is ethoxycarbonyl ($-COOC_2H_5$), claim 1 reads on etretinate, esters and pharmaceutically acceptable salts thereof.

Claim 2, in an edited form, reads as follows:

2. A compound of the formula:



wherein R_1 and R_2 are lower alkyl; R_3 is . . . lower alkyl; R_4 is lower alkoxy; R_5 is hydrogen . . .; and R_6 is . . . alkoxycarbonyl . . ., or pharmaceutically salts thereof.

Etretinate has the chemical structure identified above. When in claim 2, R_1, R_2 and R_3 each are methyl, R_4 is methoxy and R_6 is alkoxycarbonyl and in particular R_6 is ethoxycarbonyl ($-COOC_2H_5$), claim 2 reads on etretinate, esters and pharmaceutically acceptable salts thereof.

Claim 3 reads as follows:

3. The compound of claim 1 wherein R_6 is alkoxycarbonyl.

Since in claim 3 (which depends from claim 1), R_6 is alkoxycarbonyl which includes ethoxycarbonyl ($-COOC_2H_5$) and R_1-R_5 are as described above with regard to claim 1, claim 3 reads on etretinate, esters and pharmaceutically acceptable salts thereof.

Claim 5 reads:

5. The compound of claim 3 wherein said compound is 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester.

Etretinate has the chemical formula ethyl-(all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraenoate, which is the all E (trans) isomer for the compound named in claim 5. Accordingly, claim 5 (which depends from claim 1) reads on etretinate and pharmaceutically acceptable salts thereof.

Accordingly, claims 1, 2, 3 and 5 of U.S. Patent No. 4,215,215 read on etretinate, its esters and its pharmaceutically acceptable salts.

(9) The Relevant Dates And Information Pursuant To 35 U.S.C. Sec. 156(g) In Order To Enable The Secretary Of Health and Human Services To Determine The Applicable Regulatory Review Period

a) September 10, 1976 - Roche mailed a Notice of Claimed Investigational Exemption for a New Drug ("IND") for etretinate (Ro 10-9359) under Section 505(i) of FD&C to permit interstate shipment of etretinate for the purposes of conducting clinical studies to support the approval of a subsequent NDA. (Exhibit 3)

b) September 14, 1976 - In a letter of September 21, 1976, FDA acknowledged receipt on September 14, 1976 of the IND for etretinate and assigned the IND number 12,797. (Exhibit 4)

c) October 14, 1976 - The date Roche's IND for etretinate became effective, thus establishing the beginning of the portion of the regulatory review period under 35 USC 156(g)(1)(B)(i).

d) July 29, 1980 - U.S. Patent No. 4,215,215 claiming etretinate issued. (Exhibit 2)

e) December 19, 1984 - Roche hand delivered to the FDA an original New Drug Application ("NDA") for etretinate pursuant to Section 505 of FD&C and a cover letter dated December 20, 1984. This submission, thus established the end of the portion of the regulatory review period defined under 35 USC 156(g)(1)(B)(i) and the beginning of the remaining portion of the regulatory review period defined under 35 USC 156(g)(1)(B)(ii). (Exhibit 5)

f) December 24, 1984 - FDA acknowledges receipt on December 20, 1984 of Roche's NDA for etretinate and confirmed the assignment of application number 19-369. (Exhibit 6)

g) September 30, 1986 - FDA forwarded a letter indicating that FDA has completed its review of NDA number 19-369 for etretinate and has concluded that the drug is safe and effective for use as recommended in the final printed labeling. (Exhibit 7). Accordingly, the application was approved.

(10) A Brief Description Of The Activities Undertaken By The Applicant During The Applicable Regulatory Review Period With Respect To The Approved Product And The Significant Dates Applicable To Such Activities

A chronology of communications involving Roche and the FDA during the regulatory review period is attached as Exhibit 8. This exhibit lists the date, type of communication and a brief summary of the contents of the communication. This chronology provides a description of the activities undertaken by Roche during the applicable review period. For convenience, the chronology is divided into a Testing Phase and an Application Phase.

(11) A Statement That In The Opinion Of The Applicant The Patent Is Eligible For The Extension And A Statement As To The Length Of The Extension Claimed, Including How The Length Of Extension Was Determined

Under the law and in the opinion of applicant, U.S. Patent No. 4,215,215 is eligible for an extension under 35 USC 156. In particular, 35 USC 156(a) (and Section B of the initial

guidelines) in their relevant parts, provide that the term of a patent shall be extended if the following requirements are satisfied: 1. the patent claims a product, a method of using a product or a method of manufacturing a product; 2. the term of the patent has not expired before an application for extension is submitted; 3. the term of the patent has never been extended; 4. an application for extension is submitted by the owner of record of the patent or its agent and in accordance with 35 USC 156(d); 5. the product has been subject to a regulatory review period as defined in 35 USC 156(a) before its commercial marketing or use; and 6. the permission for the commercial marketing or use of the product after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

These requirements are met as follows:

1. U.S. Patent No. 4,215,215 claims a product.
2. The term of U.S. Patent No. 4,215,215 presently will expire on July 29, 1997 and thus, the patent has not expired before submission of this Application.
3. The term of U.S. Patent No. 4,215,215 has never been extended under 35 USC 156.
4. This Application is submitted by Roche, the owner of record of U.S. Patent No. 4,215,215. This Application is submitted in accordance with 35 USC 156(d) within the sixty day period beginning on September 30, 1986

and ending November 29, 1986. The product received permission for marketing or use under FD&C. This Application contains the information required under 35 USC 156(d).

5. The product was subject to a regulatory review period under Sections 505 of the FD&C before its commercial marketing or use, as evidenced by the chronology (Exhibit 8) and the September 30, 1986 letter from the FDA (Exhibit 7).

6. The permission for the commercial marketing of etretinate, the active ingredient in Tegison® oral, after the regulatory review period is the first permitted commercial marketing or use of a product having etretinate in any form as its active ingredient, under the provisions of the FD&C under which such regulatory review period occurred. This is confirmed by the absence of any approved new drug application for etretinate prior to September 30, 1986.

Accordingly, U.S. Patent No. 4,215,215 satisfies the requirements for an extension under 35 USC 156.

In the opinion of the Applicant, the term of U.S. Patent No. 4,215,215 should be extended for a period of two years from July 29, 1997 to July 29, 1999.

This extension was determined on the following basis:

Testing Phase

For the approved product, that portion of the regulatory review period as defined in 35 USC 156(g)(1)(B)(i) ("Testing Phase") commenced on October 14, 1976 and ended on December 19, 1984, which is 2988 days.

Application Phase

For the approved product, that portion of the regulatory review period as defined under 35 USC 156(g)(1)(B)(ii) ("Application Phase") commenced on December 19, 1984 and ended on September 30, 1986, which is 650 days.

Regulatory Review Period

As defined in 35 USC 156(g)(1)(B), the regulatory review period is the sum of the Testing Phase and the Application Phase, which is a total of 3638 days.

Pre-Patent Issuance Reduction to Regulatory Review Period

Under 35 USC 156(c), inter alia, the term of the patent eligible for extension is extended by that portion of the regulatory review period for the approved product which occurs after the date the patent issues. The patent issued July 29, 1980, during the Testing Phase. The Testing Phase and the regulatory review period, thus, are reduced by the time from October 14, 1976 through July 29, 1980, which is 1384 days. The Testing Phase is reduced to 1604 days and the regulatory review period is reduced to 2254 days.

Due Diligence Reduction to Regulatory Review Period

Under 35 USC 156(c)(1), the Testing Phase and Application Phase of the regulatory review period also are reduced by the period in which the applicant for the patent extension did not act with due diligence during such period of the regulatory review period. In the opinion of the Applicant, it acted with due diligence during both periods of time, and thus there is no reduction in the regulatory review period because of lack of due diligence.

One-Half Testing Phase Reduction

Under 35 USC 156(c)(2), the 2254 day revised regulatory review period is reduced by one-half of the 1604 day revised Testing Phase. One-half of the revised Testing Phase is 802 days. Thus, the 2254 day regulatory review period is reduced by 802 days leaving a final revised regulatory review period of 1452 days.

14 Year Cap

Under 35 USC 156(c)(3) should the period of time remaining in the term of the patent after the date of approval when added to the period of extension exceed fourteen years, the period of extension is reduced so that the total of both such periods does not exceed fourteen years. In applying this section, the final revised regulatory review period as calculated above (1452 days) is added onto the end of the original term of the patent (July 29, 1997) thus, giving a date of July 20, 2001. Also, fourteen years is added to the NDA approval date (September 30, 1986) thus giving a date of September 30, 2000.

The earlier of the above two dates, September 30, 2000, is selected.

Two Year Maximum Extension

Under 35 USC 156(g)(4)(C), since U.S. Patent No. 4,215,215 issued before September 24, 1984 (the date of the enactment of 35 USC 156) and since the IND was submitted before September 24, 1984 with respect to the approved product, and the commercial marketing or use of the product had not been approved before such date, the period of extension determined on the basis of the regulatory review period may not exceed two years.

Accordingly, one adds two (2) years to the original patent expiration date of July 29, 1997 to obtain an expiration date of July 29, 1999. One then compares this date with the September 30, 2000 date obtained above with regard to the 14 year cap, and chooses the earlier date, that is, July 29, 1999.

The term of U.S. Patent No. 4,215,215, thus, is eligible for a two (2) year extension, from July 29, 1997 to July 29, 1999.

(12) A Statement That Applicant Acknowledges A Duty To Disclose To The Commissioner Of Patents And Trademarks And The Secretary Of Health And Human Services Any Information Which Is Material To Any Determinations To Be Made Relative To The Application For Extension

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademark and the Secretary of

Health and Human Services any information which is material to any determinations to be made relative to the application for extension.

In addition to the information provided herein, Applicant notes as follows:

Roche is conducting research to consider developing etretinate in a topical formulation. Applicant petitions for this extension of U.S. Patent No. 4,215,215, inter alia, to apply to all formulations of etretinate, as well as to esters and pharmaceutically acceptable salts of etretrinate covered by U.S. Patent No. 4,215,215, as a single ingredient or in combination with another active ingredient.

(13) The Prescribed Fee for Receiving and Acting Upon the Application for Extension...and an Oath or Declaration As Set Forth in Paragraph C of this Section

Applicant encloses (in duplicate) a transmittal letter requesting the amount of $750.00 be charged to Account No. 08-2525.

Applicant attaches a declaration as set forth in paragraph C of the initial guidelines, signed by an officer of Roche, the owner of record of U.S. Patent No. 4,215,215.

Request for Extension

Having included in this Application all of the requisite information required under 35 U.S.C. 156 and the initial Patent and Trademark Office Guidelines published at 1047 O.G. 17, Applicant requests an extension of U.S. Patent No. 4,215,215 for two years from July 29, 1997 to July 29, 1999, by reason of claims to etretinate, including esters and pharmaceutically acceptable salts thereof.

Respectfully submitted,

HOFFMANN-LA ROCHE INC.

By 

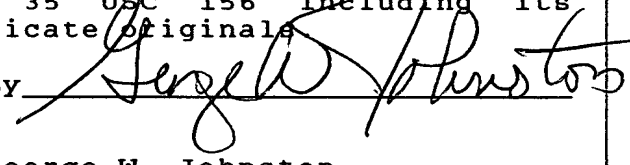
George W. Johnston
Name (Print)

Senior Patent Counsel
Title

November 7, 1986
Date

Certification

The undersigned certifies that this Application for Extension of Patent Term Under 35 USC 156 including its exhibits is being submitted as duplicate originals.

By 

George W. Johnston
Name (Print)

Senior Patent Counsel
Title

November 7, 1986
Date

3076P

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NOV 21 1986
PAT. & TRADEMARK OFF.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent 4,215,215

WERNER BOLLAG, RUDOLF RUEGG and GOTTLIEB RYSER

Attn: Box Patent Ext.

Issue Date: July 29, 1980

For: 9-PHENYL-NONATE TETRAENE COMPOUNDS

TRANSMITTAL LETTER FOR
APPLICATION FOR EXTENSION OF PATENT TERM
UNDER 35 USC 156

Nutley, New Jersey 07110
November 7, 1986

Honorable Commissioner of Patents & Trademarks

Washington, D.C. 20231

S i r:

Transmitted herewith is the a) Application for Extension of Patent Term Under 35 USC 156 and b) Declaration and Power of Attorney with regard to U.S. Patent No. 4,215,215. The application is being submitted in duplicate, and the undersigned certifies that each copy of the attached application is a duplicate original.

Please charge Deposit Account No. 08-2525 in the amount of $750.00. The Commissioner is authorized to charge any additional fees, which may be required, or credit any overpayments to Account No. 08-2525.

CERTIFICATE OF MAILING
By EXPRESS MAIL

Mailing Label Number B 28074575
Date of Deposit Nov. 21, 1986

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Print Name Mark E. Waddell

Signature Mark E. Waddell

A duplicate copy of this cover sheet is enclosed.

The Patent Office is hereby authorized to call the undersigned attorney of record "collect" on any matter connected with this application. The telephone number is Area Code (201) 235-3656. In the absence of the undersigned attorney of record, the call will be accepted by another attorney empowered in this application.

Respectfully submitted,

Attorney for Applicant

George W. Johnston
(Reg. No. 28090)
340 Kingsland Street
Nutley, New Jersey 07110

GWJ:jd
In Duplicate
3075P

MAIL ROOM
NOV 21 1986
PAT. & TRADEMARK OFF.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent 4,215,215

WERNER BOLLAG, RUDOLF RUEGG and GOTTLIEB RYSER

Attn: Box Patent Ext.

Issue Date: July 29, 1980

For: 9-PHENYL-NONATE TETRAENE COMPOUNDS

DECLARATION AND POWER OF ATTORNEY
FOR APPLICATION FOR EXTENSION OF PATENT TERM
UNDER 35 USC 156

Nutley, New Jersey 07110
November 7, 1986

Honorable Commissioner of Patents & Trademarks

Washington, D.C. 20231

S i r:

I, Jon S. Saxe, a Vice President of Hoffmann-La Roche Inc. ("Roche"), the owner of record of U.S. Patent No. 4,215,215, which submits the attached Application for Extension of Patent Term Under 35 USC 156, declare that:

(i) I have reviewed and understand the contents of the Application being submitted for extension of the term of U.S. Patent No. 4,215,215;

(ii) I believe that said patent is subject to extension under 35 USC 156;

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Print Name Mark E. Waddell

Signature Mark E. Waddell

(iii) I believe an extension of the length claimed is fully justified under 35 USC 156; and

(iv) I believe that the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 USC 156, and in particular, Section B of the initial guidelines.

I hereby appoint the following attorneys as agents for Roche under 35 USC 156 with the authority to sign, submit and prosecute this Application and transact all business in the Patent and Trademark Office and with the Secretary of Health and Human Services connected therewith. Jon S. Saxe (Reg. No. 19951), Bernard S. Leon (Reg. No. 20756), George M. Gould (Reg. No. 20970), William H. Epstein (Reg. No. 20008), William G. Isgro (Reg. No. 22041), Mark E. Waddell (Reg. No. 31803) and George W. Johnston (Reg. No. 28090).

Send correspondence to:

Jon S. Saxe
340 Kingsland Street
Nutley, New Jersey 07110

Direct Telephone Calls to: George W. Johnston
(201) 235-3656

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false

statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this patent extension application and any extension of U.S. Patent No. 4,215,215.

Respectfully submitted,

Hoffmann-La Roche Inc.

By _____

Jon S. Saxe
Name

Vice President
Title

Date November 7, 1986

3074P

MAIL ROOM
NOV 21 1986
PAT. & TRADEMARK OFF.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent 4,215,215

WERNER BOLLAG, RUDOLF RUEGG and GOTTLIEB RYSER

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S 20001 12/03/86 4215215 08-2525 020 111 750.00CH refund 200.00

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Print Name Mark E. Waddell

Signature Mark E. Waddell

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Respectfully submitted,

Attorney for Applicant

George W. Johnston
(Reg. No. 28090)
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S i r:

I, Jon S. Saxe, a Vice President of Hoffmann-La Roche Inc. ("Roche"), the owner of record of U.S. Patent No. 4,215,215, which submits the attached Application for Extension of Patent Term Under 35 USC 156, declare that:

(i) I have reviewed and understand the contents of the Application being submitted for extension of the term of U.S. Patent No. 4,215,215;

(ii) I believe that said patent is subject to extension under 35 USC 156;

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(iii) I believe an extension of the length claimed is fully justified under 35 USC 156; and

(iv) I believe that the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 USC 156, and in particular, Section B of the initial guidelines.

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Send correspondence to:

Jon S. Saxe
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I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false

statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this patent extension application and any extension of U.S. Patent No. 4,215,215.

Respectfully submitted,

Hoffmann-La Roche Inc.

By _____

Jon S. Saxe
Name

Vice President
Title

Date November 7, 1986

3074P

In re United States Patent 4,215,215

WERNER BOLLAG, RUDOLF RUEGG AND
GOTTLIEB RYSER

Issue Date: July 29, 1980

For: 9-PHENYL-NONATE TETRAENE COMPOUNDS

EXHIBITS FOR APPLICATION FOR
EXTENSION OF PATENT TERM UNDER 35 USC 156

CERTIFICATE OF MAILING
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Mailing Label Number B 280 74 575

Date of Deposit Nov. 21, 1986.

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Print Name Mark E. Waddell

Signature Mark E. Waddell

11/7/86

EXHIBIT 1

TEGISON®

brand of

etretinate/Roche

CAPSULES

ROCHE®

CONTRAINDICATION: Tegison must not be used by females who are pregnant, who intend to become pregnant, or who are unreliable or may not use reliable contraception while undergoing treatment. The period of time during which pregnancy must be avoided after treatment is concluded has not been determined. Tegison blood levels of 0.5 to 12 ng/mL have been reported in 5 of 47 patients in the range of 2.1 to 2.9 years after treatment was concluded. The length of time necessary to wait after discontinuation of treatment to assure that no drug will be detectable in the blood has not been determined. The significance of undetectable blood levels relative to the risk of teratogenicity is unknown.

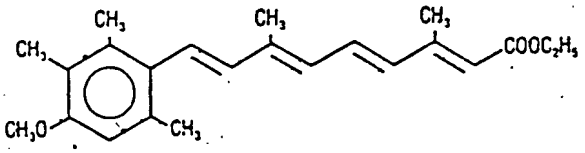
Major human fetal abnormalities related to Tegison administration have been reported, including meningomyelocoele, meningoencephalocoele, multiple synostoses, facial dysmorphia, syndactylies, absence of terminal phalanges, malformations of hip, ankle and forearm, low set ears, high palate, decreased cranial volume, and alterations of the skull and cervical vertebrae on x-ray.

Women of childbearing potential must not be given Tegison until pregnancy is excluded. It is strongly recommended that a pregnancy test be performed within two weeks prior to initiating Tegison therapy. Tegison therapy should start on the second or third day of the next normal menstrual period. An effective form of contraception must be used for at least one month before Tegison therapy, during therapy and following discontinuation of Tegison therapy for an indefinite period of time.

Females should be fully counseled on the serious risks to the fetus should they become pregnant while undergoing treatment or after discontinuation of therapy. If pregnancy does occur, the physician and patient should discuss the desirability of continuing the pregnancy.

DESCRIPTION: Tegison (brand of etretinate/Roche), a retinoid, is available in 10-mg and 25-mg gelatin capsules for oral administration. Each capsule also contains corn starch, lactose and talc. Gelatin capsule shells contain parabens (methyl and propyl) and potassium sorbate, with the following dye systems: 10 mg—iron oxide (yellow, black and red), FD&C Blue No. 2 and titanium dioxide; 25 mg—iron oxide (yellow, black and red) and titanium dioxide.

Chemically, etretinate is ethyl (*all-E*)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoate and is related to both retinoic acid and retinol (vitamin A). It is a greenish-yellow to yellow powder with a calculated molecular weight of 354.5. The structural formula is:



CLINICAL PHARMACOLOGY: The mechanism of action of Tegison is unknown.

Clinical: Improvement in psoriatic patients occurs in association with a decrease in scale, erythema and thickness of lesions, as well as histological evidence of normalization of epidermal differentiation, decreased stratum corneum thickness and decreased inflammation in the epidermis and dermis.

Pharmacokinetics: The pharmacokinetic profile of etretinate is predictable and is linear following single and multiple doses. Etretinate is extensively metabolized following oral dosing, with significant first-pass metabolism to the acid form, which also has the all-*trans* structure and is pharmacologically active. Subsequent metabolism results in the 13-*cis* acid form, chain-shortened breakdown products and conjugates that are ultimately excreted in the bile and urine.

After a six-month course of therapy with doses ranging from 25 mg once daily to 25 mg four times daily, Cmax values ranged from 102 to 389 ng/mL and occurred at Tmax values of two to six hours. In one study the apparent terminal half-life after six months of therapy was approximately 120 days. In another study of 47 patients treated chronically with etretinate, 5 had detectable serum drug levels (in the range of 0.5 to 12 ng/mL) 2.1 to 2.9 years after therapy was discontinued. The long half-life appears to be due to storage of etretinate in adipose tissue.

Etretinate is more than 99% bound to plasma proteins, predominantly lipoproteins, whereas its active metabolite, the all-*trans* acid form, is predominantly bound to albumin. Concentrations of etretinate in blister fluid after six weeks of dosing were approximately one-tenth of those observed in plasma. Concentrations of etretinate and its all-*trans* acid metabolite in epidermal specimens obtained after 1 to 36 months of therapy were a function of location; subcutis>>serum> epidermis>dermis. Similarly, liver concentrations of etretinate in patients receiving therapy for six months were generally higher than concomitant plasma concentrations and tended to be higher in livers with a higher degree of fatty infiltration.

Studies in normal volunteers indicated that, when compared with the fasting state, the absorption of etretinate was increased by whole milk or a high-lipid diet.

INDICATIONS AND USAGE: Tegison is indicated for the treatment of severe recalcitrant psoriasis, including the erythrodermic and generalized pustular types. Because of significant adverse effects associated with its use, Tegison should be prescribed only by physicians knowledgeable in the systemic use of retinoids and reserved for patients with severe recalcitrant psoriasis who are unresponsive to or intolerant of standard therapies: topical tar plus UVB light; psoralens plus UVA light; systemic corticosteroids; and methotrexate.

The use of Tegison resulted in clinical improvement in the majority of patients treated. Complete clearing of the disease was observed after four to nine months of therapy in 13% of all patients treated for severe psoriasis. This included complete clearing in 16% of patients with erythrodermic psoriasis and 37% of patients with generalized pustular psoriasis.

After discontinuation of Tegison the majority of patients experience some degree of relapse by the end of two months. After relapse, subsequent four- to nine-month courses of Tegison therapy resulted in approximately the same clinical response as experienced during the initial course of therapy.

CONTRAINDICATIONS: Pregnancy: Category X. See boxed CONTRAINDICATION.

WARNINGS:

Pseudotumor cerebri: Tegison and other retinoids have been associated with cases of pseudotumor cerebri (benign intracranial hypertension). Early signs and symptoms of pseudotumor cerebri include papilledema, headache, nausea and vomiting, and visual disturbances. Patients with these symptoms should be examined for papilledema and, if present, they should discontinue Tegison immediately and be referred for neurologic diagnosis and care.

Hepatotoxicity: Of the 652 patients treated in U.S. clinical trials, ten had clinical or histologic hepatitis considered possibly or probably related to Tegison treatment. Liver function tests returned to normal in eight of these patients after Tegison was discontinued; one patient had histologic changes resembling chronic active hepatitis six months off therapy, and one patient had no follow-up available. There have been four reports of hepatitis-related deaths worldwide; two of these patients had received etretinate for a month or less before presenting with hepatic symptoms. Elevations of AST (SGOT), ALT (SGPT) or LDH have occurred in 18%, 23% and 15%, respectively, of individuals treated with Tegison. If hepatotoxicity is suspected during treatment with Tegison, the drug should be discontinued and the etiology further investigated.

Ophthalmic effects: Corneal erosion, abrasion, irregularity and punctate staining have occurred in patients treated with Tegison, although these effects were absent or improved after therapy was stopped in those patients who had follow-up examinations. Corneal opacities have occurred in patients receiving isotretinoin; they had either completely resolved or were resolving at follow-up six to seven weeks after discontinuation of the drug. Other ophthalmic effects that have occurred in Tegison patients include decreased visual acuity and blurring of vision, night vision decrease, minimal posterior subcapsular cataract, iritis, blot retinal hemorrhage, scotoma and photophobia. Any Tegison patient experiencing visual difficulties should discontinue the drug and have an ophthalmological examination.

Hyperostosis: In clinical trials with Tegison, 45 patients with a mean age of 40 years have been retrospectively evaluated for evidence of hyperostosis. They had received etretinate at a mean dose of 0.8 mg/kg for a mean duration of 33 months at the time of x-ray. Eleven patients had psoriasis, while 34 patients had a disorder of keratinization. Of these, 38 patients who continued to receive etretinate at an average dose of 0.8 mg/kg/day for an average duration of 60 months, 32 (84%) had radiographic evidence of extraspinal tendon and ligament calcification. The most common sites of involvement were the ankles (76%), pelvis (53%) and knees (42%); spinal changes were uncommon. Involvement tended to be bilateral and multifocal. There were no bone or joint symptoms at the sites of radiographic abnormalities in 47% of the affected patients.

Lipids: Blood lipid determinations should be performed before Tegison is administered and then at intervals of one or two weeks until the lipid response to Tegison is established; this usually occurs within four to eight weeks.

Approximately 45% of patients receiving Tegison during clinical trials experienced an elevation of plasma triglycerides. Approximately 37% developed a decrease in high density lipoproteins and about 16% showed an increase in cholesterol levels. These effects on triglycerides, HDL and cholesterol were reversible after cessation of Tegison therapy.

Patients with an increased tendency to develop hypertriglyceridemia include those with diabetes mellitus, obesity, increased alcohol intake or a familial history of these conditions.

Hypertriglyceridemia, hypercholesterolemia and lowered HDL may increase a patient's cardiovascular risk status. In addition, elevation of serum triglycerides in excess of 800 mg/dL has been associated with acute pancreatitis. Therefore, every attempt should be made to control significant elevations of triglycerides or cholesterol or significant decreases in HDL. Some patients have been able to reverse triglyceride and cholesterol elevations or HDL decrease by reduction in weight or restriction of dietary fat and alcohol while continuing Tegison therapy.

Cardiovascular effects: During clinical trials of 652 patients, 21 significant cardiovascular adverse incidents were reported, all in patients who had a strong history of cardiovascular risk. These incidents were not considered related to Tegison therapy except for two cases of myocardial infarction: one which was considered possibly related to Tegison therapy and one for which a relationship was not specified.

Animal studies: In general, the signs of etretinate toxicity in rats, mice and dogs are dose-related with respect to incidence, onset and severity. In rodents, the most striking manifestations of this toxicity are bone fractures; no evidence of fractures was observed in a one-year dog study. Other dose-related changes in some animals treated with etretinate in subchronic or chronic toxicity studies include alopecia, erythema, reductions in body weight and food consumption, stiffness, altered gait, hematologic changes, elevations in serum alkaline phosphatase and testicular atrophy with microscopic evidence of reduced spermatogenesis.

PRECAUTIONS: *Information for Patients:* Women of childbearing potential should be advised that they must not be pregnant when Tegison therapy is initiated, and that they should use an effective form of contraception for one month prior to Tegison therapy, while taking Tegison and after Tegison has been discontinued. Tegison has been found in the blood of some patients two to three years after the drug was discontinued. See boxed CONTRAINDICATION.

Because of the relationship of Tegison to vitamin A, patients should be advised against taking vitamin A supplements to avoid possible additive toxic effects.

Patients should be advised that transient exacerbation of psoriasis is commonly seen during the initial period of therapy.

Patients should be informed that they may experience decreased tolerance to contact lenses during and after therapy.

Laboratory Tests: See WARNINGS section. In clinical studies, the incidence of hypertriglyceridemia was one patient in two, that of hypercholesterolemia one patient in six, and that of decreased HDL one patient in three during Tegison therapy. Pretreatment and follow-up blood lipids should be obtained under fasting conditions. If alcohol has been consumed, at least 36 hours should elapse before these determinations are made. It is recommended that these tests be performed at weekly or biweekly intervals until the lipid response to Tegison is established.

Elevations of AST (SGOT), ALT (SGPT) or LDH have occurred in 18%, 23% and 15%, respectively, of individuals treated with Tegison. It is recommended that these tests be performed prior to initiation of Tegison therapy, at one to two week intervals for the first one to two months of therapy and thereafter at intervals of one to three months, depending on the response to Tegison administration.

Drug Interactions: Little information is available on drug interactions with Tegison; however, concomitant consumption of milk increases the absorption of etretinate. See *Pharmacokinetics* and DOSAGE AND ADMINISTRATION sections.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: In a two-year study, male or female Sprague-Dawley rats given etretinate by dietary admixture at doses up to 3 mg/kg/day (two times the maximum recommended human therapeutic dose) had no increase in tumor incidence.

In an 80-week study, Crl:CD-1 (ICR) BR mice were given etretinate by dietary admixture at doses of 1 to 5 mg/kg/day. An increased incidence of blood vessel tumors (hemangiomas and hemangiosarcomas in several different tissue sites) was noted in the high-dose male group (4 to 5 mg/kg/day) but not in the female group.

Mutagenesis: Etretinate was evaluated by the Ames test in a host-mediated assay, in the micronucleus test, and in a "treat and plate" test using the diploid yeast strain *S. cerevisiae* D7. Except for a weakly positive response in the Ames test using the tester strain TA 100, there was no evidence of genotoxicity. No differences in the rate of sister chromatid exchange (SCE) were noted in lymphocytes of patients before and after four weeks of treatment with therapeutic doses of etretinate.

Impairment of Fertility: In a study of fertility and general reproductive performance in rats, no etretinate-related effects were observed at doses up to 2.5 mg/kg/day. At a dose of 5 mg/kg/day (approximately three times the maximum recommended human therapeutic dose) the readiness of the treated animals to copulate was reduced but the pregnancy rate was unaffected. The number of viable young at birth and their postnatal weight gain and survival were adversely affected at the high dose. The pregnancy rate of the untreated first generation animals and postnatal weight gain of the untreated second generation animals were also reduced.

No adverse effects on sperm production were noted in 12 psoriatic patients given 75 mg/day of etretinate for one month and 50 mg/day for an additional two months. However, testicular atrophy was noted in subchronic and chronic rat studies and in a chronic dog study, in some cases at doses approaching those recommended for use in humans. Decreased sperm counts were reported in a 13-week dog study at doses as low as 3 mg/kg/day (approximately twice the maximum recommended human dose). Spermatogenic arrest also was reported with chronic administration of the all-*trans* metabolite to dogs.

Pregnancy: Category X. See boxed CONTRAINDICATION.

The following limited preliminary data must not be read or understood to diminish the serious risk of teratogenicity set forth in the boxed pregnancy CONTRAINDICATION.

Thirty women worldwide have been reported as having taken one or more doses of Tegison during pregnancy. In 29 cases in which information was available, there were a total of ten congenital abnormalities. The occurrence of congenital abnormalities was four of 20 among delivered infants, two of two among spontaneously aborted fetuses, and four of seven among induced abortions.

A further 38 women are reported to have become pregnant within 24 months after discontinuing Tegison therapy. Because congenital abnormalities have been reported in these pregnancies, it cannot be stated that there is a "safe" time to become pregnant after Tegison therapy. In 37 cases in which information was available, there were a total of three congenital abnormalities. The occurrence of congenital abnormalities was two of 29 among delivered infants, zero of one among spontaneously aborted fetuses, and one of five among induced abortions. Two stillbirths with no apparent congenital abnormalities were attributed to other causes.

Nonteratogenic Effects: No adverse effects on various parameters of late gestation and lactation were observed in rats at doses of etretinate up to 4 mg/kg/day (approximately three times the maximum human recommended dose). At doses of 8 mg/kg/day (approximately five times the maximum human recommended dose) of etretinate, the rate of stillbirths was increased and neonatal weight gain and survival rate were markedly reduced.

Nursing Mothers: Studies have shown that etretinate is excreted in the milk of lactating rats; however, it is not known whether this drug is excreted in human milk. Because of the potential for adverse effects, nursing mothers should not receive Tegison.

Pediatric Use: No clinical studies have been conducted in the U.S. using Tegison in children. Ossification of interosseous ligaments and tendons of the extremities has been reported. Two children showed x-ray changes suggestive of premature epiphyseal closure during treatment with Tegison. Skeletal hyperostosis has also been reported after treatment with isotretinoin. It is not known if any of these effects occur more commonly in children, but concern should be greater because of the growth process. Pretreatment x-rays for bone age including x-rays of the knees, followed by yearly monitoring, are advised. In addition, pain or limitation of motion should be evaluated with appropriate radiological examination. Because of the lack of data on the use of etretinate in children and the possibility of their being more sensitive to effects of the drug, this product should be used only when all alternative therapies have been exhausted.

ADVERSE EVENTS: *Clinical:* Hepatitis was observed in about 1.5% of patients treated with Tegison in clinical trials. See WARNINGS section.

Tegison has been associated with pseudotumor cerebri. See WARNINGS section.

Hypervitaminosis A produces a wide spectrum of signs and symptoms of primarily the mucocutaneous, musculoskeletal, hepatic and central nervous systems. Nearly all of the clinical adverse events reported to date with Tegison administration resemble those of the hypervitaminosis A syndrome. Table I lists the adverse events frequently reported during clinical trials in which 652 patients were treated either for psoriasis (591 patients) or a disorder of keratinization (61 patients). Table II lists less frequently reported adverse events in these same patients.

TABLE I
ADVERSE EVENTS FREQUENTLY REPORTED DURING CLINICAL TRIALS
PERCENT OF PATIENTS REPORTING (N = 652)

BODY SYSTEM	>75%	50-75%	25-50%	10-25%
Mucocutaneous	Dry nose Chapped lips	Excessive thirst Sore mouth	Nosebleed	Cheilitis Sore tongue
Dermatologic	Loss of hair Palm/sole/ fingertip peeling	Dry skin Itching Rash Red scaly face Skin fragility	Bruising Sunburn	Nail disorder Skin peeling
Musculoskeletal		Bone/joint pain	Muscle cramps	
Central Nervous		Fatigue	Headache	Fever
Special Senses		Irritation of eyes	Eyeball pain Eyelid abnormalities	Abnormalities of: –conjunctiva –cornea –lens –retina Conjunctivitis Decrease in visual acuity Double vision
Gastrointestinal			Abdominal pain Changes in appetite	Nausea

TABLE II

LESS FREQUENT ADVERSE EVENTS REPORTED DURING CLINICAL TRIALS
(SOME OF WHICH MAY BEAR NO RELATIONSHIP TO THERAPY)
PERCENT OF PATIENTS REPORTING (N = 652)

BODY SYSTEM	1-10%	<1%
Mucocutaneous	Dry eyes Mucous membrane abnormalities Dry mouth Gingival bleeding/inflammation	Decreased mucus secretion Rhinorrhea
Dermatologic	Hair abnormalities Bullous eruption Cold/clammy skin Onycholysis Paronychia Pyogenic granuloma Changes in perspiration	Abnormal skin odor Granulation tissue Healing impairment Herpes simplex Hirsutism Increased pore size Sensory skin changes Skin atrophy Skin fissures Skin infection Skin nodule Skin ulceration Urticaria
Musculoskeletal	Myalgia	Gout Hyperkinesia Hyperostosis Hypertonia
Central Nervous System	Dizziness Lethargy Changes in sensation Pain Rigors	Abnormal thinking Amnesia Anxiety Depression Pseudotumor cerebri Emotional lability Faint feeling Flu-like symptoms
Special Senses	Abnormal lacrimation Abnormal vision Abnormalities of: –Extraocular musculature –Ocular tension –Pupil –Vitreous Earache Otitis externa	Change in equilibrium Ear drainage Ear infection Hearing change Night vision decrease Photophobia Visual change Scotoma
Gastrointestinal	Hepatitis	Constipation Diarrhea Melena Flatulence Weight loss Oral ulcers Taste perversion Tooth caries
Cardiovascular	Cardiovascular thrombotic or obstructive events Edema	Atrial fibrillation Chest pain Coagulation disorder Phlebitis Postural hypotension Syncope
Respiratory	Dyspnea	Coughing Increased sputum Dysphonia Pharyngitis
Renal		Kidney stones
Urogenital		Abnormal menses Atrophic vaginitis Dysuria Polyuria Urinary retention
Other	Malignant neoplasms	

Laboratory: Tegison therapy induces change in serum lipids in a significant number of treated patients. Approximately 45% of patients experienced elevation in serum triglycerides, 37% a decrease in high density lipoproteins and 16% an increase in cholesterol levels.

Approximately 46% of patients had elevations of triglycerides above 250 mg/dL, 54% had decreases of HDL below 36 mg%, and 19% had elevations of cholesterol above 300 mg%. One case of eruptive xanthomas associated with triglyceride levels greater than 1000 mg% has been reported.

Elevations of AST (SGOT), ALT (SGPT) or LDH were experienced by 18%, 23% and 15%, respectively, of individuals treated with Tegison. In most of the patients, the elevations were slight to moderate and became normal either during therapy or after cessation of treatment. See WARNINGS section.

Table III lists the laboratory abnormalities reported during clinical trials. Data for patients who received intermittent courses of therapy for periods up to five years are included. Any instance of two consecutive values outside the range of normal, or an abnormal value with no follow-up during therapy, was considered to be possibly related to Tegison.

TABLE III
LABORATORY ABNORMALITIES REPORTED DURING CLINICAL TRIALS
PERCENT OF PATIENTS REPORTING

BODY SYSTEM	25-50%	10-25%	1-10%
Hematologic	Increased: –MCHC (60%) –MCH –Reticulocytes –PTT –ESR	Decreased: –Hemoglobin/HCT –RBC –MCV Increased platelets Increased or decreased: –WBC and components –Prothrombin time	Decreased: –Platelets –MCH –MCHC –PTT Increased: –Hemoglobin/HCT –RBC
Urinary		WBC in urine	Proteinuria Glycosuria Microscopic hematuria Casts in urine Acetonuria Hemoglobinuria
Hepatic	Increased triglycerides	Increased: –AST (SGOT) –ALT (SGPT) –Alkaline phosphatase –GGTP –Globulin –Cholesterol	Increased bilirubin Increased or decreased: –Total protein –Albumin
Renal			Increased: –BUN –Creatinine
Electrolytes	Increased or decreased potassium	Increased or decreased: –Venous CO_2 –Sodium –Chloride	
Miscellaneous	Increased or decreased: –Calcium –Phosphorus	Increased or decreased FBS	Increased CPK

OVERDOSAGE: There has been no experience with acute overdosage in humans.

The acute oral and intraperitoneal toxicities (LD_{50}) of etretinate capsules in mice and rats were greater than 4000 mg/kg. The acute oral toxicity (LD_{50}) of etretinate substance in 4% solution was 2300 mg/kg in mice and 1300 mg/kg in rats.

DOSAGE AND ADMINISTRATION: There is intersubject variation in the absorption and the rate of metabolism of Tegison. Individualization of dosage is required to achieve the maximal therapeutic response with a tolerable degree of side effects. Therapy with Tegison should generally be initiated at a dosage of 0.75 to 1 mg/kg of body weight/day taken in divided doses. A maximum dose of 1.5 mg/kg/day should not be exceeded. Erythrodermic psoriasis may respond to lower initial doses of 0.25 mg/kg/day increased by 0.25 mg/kg/day each week until optimal initial response is attained.

Maintenance doses of 0.5 to 0.75 mg/kg/day may be initiated after initial response, generally after 8 to 16 weeks of therapy. In general, therapy should be terminated in patients whose lesions have sufficiently resolved. Relapses may be treated as outlined for initial therapy.

Tegison should be administered with food.

HOW SUPPLIED: Brown and green capsules, 10 mg, imprinted TEGISON 10 ROCHE; Prescription Paks of 30 (NDC 0004-0177-57).

Brown and caramel capsules, 25 mg, imprinted TEGISON 25 ROCHE; Prescription Paks of 30 (NDC 0004-0179-57).

STORE AT 59° TO 86°F; 15° TO 30°C. PROTECT FROM LIGHT.

THIS PACKAGE INSERT ISSUED SEPTEMBER 1986.

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

13-06-71200-0986

Printed in U.S.A.

EXHIBIT 2

United States Patent [19]

Bollag et al.

[11] **4,215,215**

[45] **Jul. 29, 1980**

[54] **9-PHENYL-NONATE TRAENE COMPOUNDS**

[75] Inventors: **Werner Bollag**, Basel; **Rudolf Ruegg**, Bottmingen; **Gottlieb Ryser**, Basel, all of Switzerland

[73] Assignee: **Hoffmann-La Roche Inc.**, Nutley, N.J.

[21] Appl. No.: **55,437**

[22] Filed: **Jul. 6, 1979**

Related U.S. Application Data

[60] Continuation of Ser. No. 903,438, May 8, 1978, abandoned, which is a division of Ser. No. 714,170, Aug. 13, 1976, Pat. No. 4,105,681, which is a continuation-in-part of Ser. No. 601,148, Aug. 1, 1975, abandoned, which is a continuation-in-part of Ser. No. 454,007, Mar. 22, 1974, abandoned.

[51] **Int. Cl.**[2] **C09F 5/00**; C11C 3/00; C09F 5/08; C07D 207/04

[52] **U.S. Cl.** ..... **542/427**; 542/438; 260/404; 260/404.5; 260/410.9 R; 260/410.9 N; 260/410; 260/326.8; 560/250; 560/251; 560/254; 544/86; 544/87; 544/166; 544/168; 544/172; 544/174; 546/340; 546/342; 546/232; 546/238; 546/208; 546/186; 546/190; 546/265

[58] **Field of Search** ..... 260/404, 404.5, 410.9 R, 260/410.9 N, 410 R, 326.8; 560/250, 251, 254; 544/166, 172, 168, 174, 86, 87; 546/340, 186, 342, 190, 232, 265, 238, 208; 542/427, 438

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Lowe et al., J. Org. Chem. Soc., pp. 1855-1861, (1958).

Primary Examiner—John F. Niebling
Attorney, Agent, or Firm—Jon S. Saxe; Bernard S. Leon; George W. Johnston

[57] **ABSTRACT**

Novel 9-phenyl 5,6-dimethyl-nona-2,4,6,8-tetraenoic acid, tetraenal or tetraenol derivatives useful as anti-tumor agents.

30 Claims, No Drawings

9-PHENYL-NONATE TRAENE COMPOUNDS

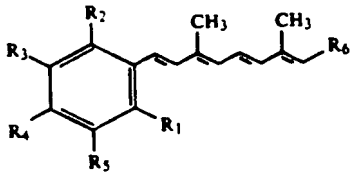
CROSS REFERENCE TO RELATED APPLICATIONS

This is a continuation of application Ser. No. 903,438, filed May 8, 1978, now abandoned, which in turn is a division of Ser. No. 714,170, filed Aug. 13, 1976, now U.S. Pat. No. 4,105,681, which in turn is a continuation-in-part of prior application Ser. No. 601,148, filed Aug. 1, 1975, now abandoned, which in turn is a continuation-in-part of Ser. No. 454,007, filed Mar. 22, 1974, now abandoned.

SUMMARY OF THE INVENTION

In accordance with this invention, it has been found that compounds of the formula:

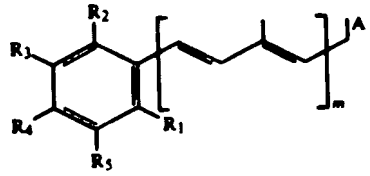
I



wherein R_1 and R_2 are lower alkyl; R_3 is hydrogen, lower alkyl, lower alkoxy, lower alkenyloxy, nitro, halo, amino, lower alkyl-amino, lower alkanoylamino, or N-heterocyclyl; R_4 is hydrogen, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, nitro, lower alkanoyloxy, amino, lower alkylamino or N-heterocyclyl; R_5 is hydrogen, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, nitro, halo, amino, lower alkanoylamino, lower alkyl amino, or N-heterocyclyl; with the proviso that at least one of R_3, R_4, and R_5 is other than hydrogen; with the further proviso that when R_3 or R_5 is halogen, R_4 is other than alkoxy; R_6 is formyl, hydroxymethylene, alkoxymethylene, alkanoyloxymethylene, carboxyl, alkoxycarbonyl, alkenloxycarbonyl, alkynyloxycarbonyl, carbamoyl, mono (lower alkyl)-carbamoyl, di (lower alkyl)-carbamoyl, or N-heterocyclylcarbonyl;
or pharmaceutically acceptable salts thereof are useful as anti-tumor agents.

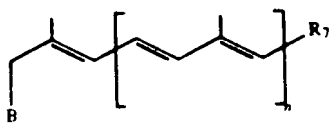
The compounds of formula I are prepared by the reaction of a compound of the formula:

II



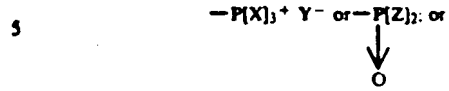
with a compound of the formula:

III

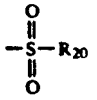


wherein R_1, R_2, R_3, R_4 and R_5 are as above; m and n are integers of from 0 to 1 with the sum of m and n being

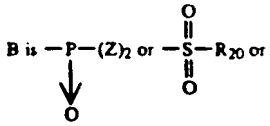
equal to 1; one of A or B being oxo and the other being:



one of A and B is

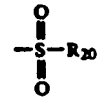


and the other being halogen, alkylsulfonyloxy or arylsulfonyloxy; X is aryl; Z is alkoxy; R_{20} is aryl, aralkenyl, aryl substituted with an electron donating or electron withdrawing group or aralkenyl where the aryl moiety is substituted with an electron withdrawing or electron donating group; R_7, when



$-P[X]_3^+Y^-$, is formyl, carboxy, alkoxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl, di (lower alkyl) carbamoyl or N-heterocyclylcarbonyl; R_7, when B is oxo, is carboxy, alkoxymethylene, alkanoyloxymethylene, alkoxycarbonyl, alkenyloxycarbonyl, alkynyloxycarbonyl or N-heterocyclylcarbonyl, R_7, when B is halogen, alkylsulfonyloxy or arylsulfonyloxy, is formyl, carboxy, alkoxymethylene, alkanoyloxymethylene, alkoxycarbonyl, alkenyloxycarbonyl; alkynyloxycarbonyl, di (lower alkyl)-amino carbamoyl, or N-heterocyclylcarbonyl, and Y is an anion of an organic or inorganic acid.

In the case where one of A or B form the sulfone group which contains this sulfone group:



This sulfone group in the reaction product can be cleaved to a double bond to form the compound of formula I. In the reaction products of the compound of formula II and III, where R_7 is a carboxyl group, this carboxyl group can be esterified or amidated. On the other hand, where R_7 is a carboxyl group or an ester group, this reaction product can be reduced to form R_7 as a hydroxy group. Where the reaction product contains R_7 as a hydroxy group, this group can be esterified or etherified. The resulting alcohol ester can, if derived, be saponified. On the other hand, where R_7 in the reaction product is a free hydroxy group or an ester group, this reaction product can be oxidized and form the corresponding compound where R_7 is carboxyl, i.e., —COOH.

DETAILED DESCRIPTION

The term "halogen", is utilized in the instant specification, denotes all four halogens, i.e., chlorine, bromide, iodine and fluorine, with chlorine and bromine being

preferred. The term "lower alkyl" denotes both straight chain and branched chain lower alkyl groups containing from 1 to 6 carbon atoms such as methyl, ethyl, isopropyl and 2-methylpropyl. The term "lower alkoxy" as used throughout this specification denotes lower alkoxy groups containing from 1 to 7 carbon atoms such as methoxy, propoxy, isopropoxy, ethoxy, etc. The term "lower alkanoyl" denotes lower alkanoyl groups containing from 2 to 6 carbon atoms such as acetyl, propionyl or pivalonyl.

The terms "lower alkenyl" and "lower alkynyl" includes both straight chain and branched chain hydrocarbon groups containing from 2 to 6 carbon atoms such as vinyl, allyl, butenyl, pentenyl, ethynyl, propargyl, butynyl, etc.

The term N-heterocyclyl designates N-heterocyclyl radicals containing preferably 5 or 6 membered rings which contain a nitrogen atom in the ring and which can, if desired, contain a further hetero atom selected from the group consisting of oxygen, nitrogen or sulfur. Among the preferred N-heterocyclyl radicals are included pyrrolidino, pyridino, piperidino, morpholino or thiomorpholino.

The lower alkanoylamino groups contain residues which are derived from lower alkanecarboxylic acids containing from 2 to 6 carbon atoms (e.g. acetic acid, propionic acid or pivalic acid).

The alkoxymethylene and alkoxycarbonyl groups preferably contain alkoxy moieties having from 1 to 6 carbon atoms. These can be straight-chain or branched-chain such as, for example, the methoxy, ethoxy and isopropoxy groups. However, the alkoxy moiety can also be a higher alkoxy group containing from 7 to 20 carbon atoms, especially the cetyloxy group. The alkoxy moiety can be substituted by functional groups; for example, by nitrogen-containing groups such as, for example, by an amino or morpholino group, which may be alkyl-substituted, or by a piperidyl or pyridyl group.

The alkenyloxycarbonyl and alkynyloxycarbonyl groups preferably contain alkenoxy and alkynoxy moieties having from 2 to 6 carbon atoms such as, for example, the allyloxy or propargyloxy group.

The term "alkanoyloxy" designates derivatives of alkanecarboxylic acids containing from 2 to 20 carbon atoms. Among the preferred lower alkanoyloxy groups are included lower alkanoyloxy groups containing from 2 to 6 carbon atoms such as acetyloxy, propionyloxy and pivalyloxy. However, the alkanoyloxy group can be derived from higher alkane carboxylic acids, i.e., acids containing from 6 to 20 carbon atoms such as palmitic acid or stearic acid as well as lower alkanoyloxy groups. The term "alkanoyloxymethylene" denotes alkanoyloxymethylene groups wherein alkanoyloxy is defined as above. Among the preferred alkanoyloxymethylene groups are included acetyloxymethylene and propionyloxymethylene.

The terms "mono" and "di (lower alkyl) carbamoyl" denote mono and di (lower alkyl) carbamoyl radicals wherein lower alkyl is defined as above. Among the preferred mono or di (lower alkyl) carbamoyl groups are included such groups as N-methyl-carbamoyl, N,N-dimethylcarbamoyl, N-isopropylcarbamoyl, and N-tertiarybutylcarbamoyl. The "N-heterocyclylcarbonyl radicals" are those which preferably contain a 5 or 6 membered heterocyclic ring, which in addition to the nitrogen atom may contain a further hetero atom selected from the group consisting of nitrogen, oxygen or sulfur. Examples of such N-heterocyclic groups which

can be utilized in accordance with this invention are included pyridino, piperidino, morpholino, thiomorpholino and pyrrolidino.

In the compound of formula I, the preferred di (lower alkyl) amino groups denoted are those where the lower alkyl substituent contains from 1 to 4 carbon atoms. Among the preferred lower alkyl amino groups are included ethyl amino, dimethyl amino, diethyl amino and diisopropyl amino. The term lower alkyl amino includes both mono and di-lower alkyl amino groups.

Among the preferred compounds of formula I are the following:

9-(2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic-acid;

9-(2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid;

9-(2,4,6-triisopropyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic-acid;

9-(2,3,4,6-tetramethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid;

9-(4-methoxy-2,6-dimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic-acid;

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid;

9-(3-methoxy-2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid;

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic-acid ethyl ester;

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2-trans,4-cis, 6-trans, 8-trans-tetraen-1-oic acid ethyl ester;

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid isopropyl ester;

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid diethylaminoethyl ester;

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid amide;

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl amide;

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid allyl ester;

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid propargyl ester;

9-(3,6-dimethoxy-2,4,5-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid;

9-(4-methoxy-3-allyl-2,6-dimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid;

9-(4-methoxy-3-nitro-2,6-dimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester;

9-(3-dimethylamino-2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester;

9-(4-isopropoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid;

9-(4-allyloxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid;

9-(5-chloro-2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid; and

9-(3-nitro-2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid.

The toxicity of the compounds of formula I is slight. For example, as will be evident from the following Table, the acute toxicity [LD_{50}] of 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid [A] and of 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester [B] in mice after intraperitoneal administration in rape-oil lies at 700 or 1000 mg/kg.

Table

Acute Toxicity			
Substance A	LD_{10} mg/kg	LD_{50} mg/kg	LD_{90} mg/kg
After 1 day	>4000	>4000	>4000
After 10 days	580	700	890
After 20 days	580	700	890
Substance B	LD_{10} mg/kg	LD_{50} mg/kg	LD_{90} mg/kg
After 1 day	>4000	>4000	>4000
After 10 days	1400	1900	2600
After 20 days	710	1000	1400

The compounds of formula I are effective for utilizing tumors such as papillomas. In the papilloma test, tumors induced with dimethylbenzanthracene and croton oil regress. The diameters of the papillomae decline within 2 weeks on intraperitoneal administration. In the case of substance A, the decline is by 38% at 50/mg/kg/week and by 69% at 100 mg/kg/week and in the case of substance B the decline is by 45% at 25 mg/kg/week and by 63% at 50 mg/kg/week.

The compounds of formula I are also useful as medicaments for the topical and systemic therapy of acne, psoriasis and other related dermatological disorders which are characterized by an increased or pathologically altered cornification, as well as inflammatory and allergic dermatological conditions. They can also be used to treat disorders which are characterized by inflammatory or degenerative alterations of the mucous membranes.

The polyene compounds of formula I can accordingly be used as medicaments; for example, in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier. The pharmaceutical preparations serving for systemic application can, for example, be produced by adding a polyene compound of formula I as the active ingredient to non-toxic, inert, solid or liquid carriers which are usual in such preparations. The pharmaceutical preparations can be administered enterally or parenterally. Suitable pharmaceutical preparations for enteral administration are, for example, tablets, capsules, dragees, syrups, suspensions, solutions and suppositories. Pharmaceutical preparations in the form of infusion or injection solutions are suitable for parenteral administration.

The dosages in which the polyene compounds of formula I can be administered can vary according to the mode of administration and route of administration as well as according to the requirements of the patient.

The polyene compounds of formula I can be administered in amounts of from 5 mg. to 200 mg. daily in one or more dosages. Capsules with a content of a ca 10 mg. to ca 100 mg. of a polyene compound are a preferred form of presentation.

The pharmaceutical preparations can contain inert or other pharmacodynamically active additives. Tablets or granules, for example, can contain a series of binding agents, fillers, carrier materials or diluents. Liquid preparations can, for example, take the form of a sterile water-miscible solution. Besides the polyene compounds of formula I, capsules can additionally contain a filling material or thickening agent. Furthermore, flavor-improving additives as well as the substances usually used as preserving, stabilizing, moisture-retaining or emulsifying agents, salts for varying the osmotic pressure, buffers and other additives can be present.

The carrier materials and diluents mentioned hereinbefore can be organic or inorganic substances; for example, water, gelatin, lactose, starches, magnesium stea-

rate, talcum, gum arabic, polyalkyleneglycols and the like. It is of course a prerequisite that all adjuvants used in the production of the pharmaceutical preparations are non-toxic.

For topical administration, the polyene compounds of formula I are expediently made up in the form of ointments, tinctures, creams, solutions, lotions, sprays, suspension and the like. Ointments and creams, as well as solutions, are preferred. These pharmaceutical preparations intended for topical administration can be produced by mixing the polyene compounds as the active ingredient with non-toxic, inert solid or liquid carriers suitable for topical administration which are usual per se in such preparations.

Expedient for topical administration are ca 0.01% to ca 0.3% (preferably 0.02% to 0.1%) solutions as well as ca 0.05% to ca 5% (preferably ca 0.1% to ca 2.0%) ointments or creams.

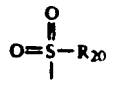
An antioxidant (e.g. tocopherol, N-methyl-γ-tocopheramine, butylated hydroxyanisole or butylated hydroxytoluen can optionally be added to the pharmaceutical preparations.

The aryl groups denoted by X in the triarylphosphonium groups of the formula $-P[X]_3^+ Y^-$ in the compounds of formula II or III include all generally known aryl groups, but especially mononuclear aryl groups such as phenyl, lower alkyl-substituted phenyl or lower alkoxy-substituted phenyl (e.g. tolyl, xylyl, mesityl and p-methoxyphenyl). Of the inorganic acid anions denoted by Y, the chloride, bromide, iodide and hydrosulphate ions are preferred and, of the organic acid anions, the tosyloxy ion is preferred.

The alkoxy groups denoted by Z in the dialkoxyphosphinyl groups of the formula

are preferably lower alkoxy groups containing from 1 to 6 carbon atoms, especially methoxy and ethoxy.

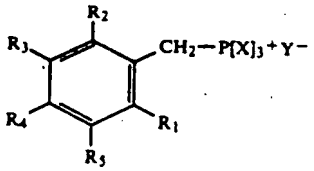
The preferred electron withdrawing groups are those which are weakly electron withdrawing. Examples of aryl and aralkenyl groups, which may be substituted by one or more electron donating to weakly electron-withdrawing substituents, denoted by R_{20} in the sulfone group of the formula:



wherein R_{20} is as above; are phenyl and styryl which may be substituted in the o-, m- or p-position by methoxy, phenoxy, acetoxy, dimethylamino, phenylmethylamino, acetylamino, thiomethyl, thiophenyl, thioacetyl, chloro, bromo or cyano or in the m-position by nitro.

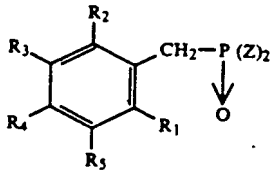
The starting materials of formulae II and III are, in part, novel compounds.

Compound of formula II where m is O and A is a triarylphosphonium group have the following formula:



II-a

wherein R_1, R_2, R_3, R_4, R_5, X and Y are as above. Compounds of the formula II where m is O and A is a dialkoxy phosphnyl group have the following formula:

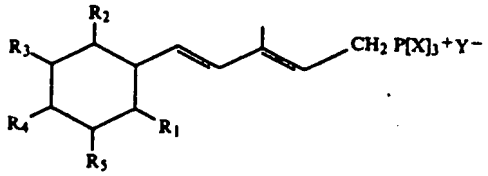


II-c

wherein R_1, R_2, R_3, R_4, R_5 and Z are as above: The compounds of formula II-a and II-c can be prepared, for example, by treating a corresponding (R_1–R_5) substituted-benzene with formaldehyde in the presence of a hydrohalic acid (e.g. concentrated hydrochloric acid), if desired in a solvent (especially glacial acetic acid) to prepare a compound of formula II where m is 0 and A is a halogen, i.e., the compound of formula II-i. The halide of formula II-i is reacted in a converted manner with a triaryl phosphine in a solvent, preferably with triphenyl phosphine in toluene or benzene, or with a trialkyl phosphite, especially with triethyl phosphite.

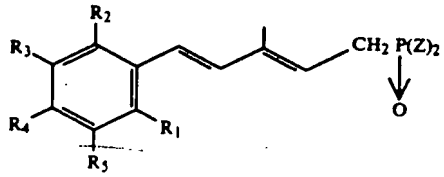
An alkoxy group present in the aforementioned (R_1–R_5)-benzene can be introduced, for example, by alkylation of a hydroxy group present. For example, the corresponding phenol can be reacted, preferably in a solvent (e.g. an alkanol) and in the presence of a base (e.g. potassium carbonate), with an alkyl halide (e.g. methyl iodide) or dimethyl sulphate.

Compounds of formula II where m is 1 and A is a triaryl phosphonium group have the formula:



II-b

wherein R_1, R_2, R_3, R_4, R_5, X and Y are as above. Compounds of formula II where m is 1 and A is dialkoxyphosphinyl have the formula:



II-d

wherein R_1, R_2, R_3, R_4, R_5 and Z is as above;

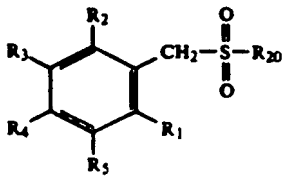
The compounds of formula II-b and II-d can be prepared by first formylating the corresponding (R_1–R_5)-benzene. This can be carried out, for example, by formylating the (R_1–R_5) substituted-benzene in the pres-

ence of a Lewis acid. As the formylating agent there can be used, in particular, an orthoformic acid ester, formyl chloride and dimethylformamide. Especially suitable Lewis acids are the halides of zinc, aluminium, titanium, tin and iron such as zinc chloride, aluminium trichloride, titanium tetrachloride, tin tetrachloride and iron trichloride as well as the halides of inorganic and organic acids such as, for example, phosphorus oxychloride and methane sulfochloride.

If the formylating agent is present in excess, the formylation may be carried out without the addition of a further solvent. In general, however, it is recommended to carry out the formylation in an inert solvent (e.g. nitrobenzene or in a chlorinated hydrocarbon such as methylene chloride). The formylation can be carried out at a temperature between 0° C. and the boiling point of the mixture.

A resulting (R_1-R_5)-benzaldehyde can subsequently be chain-lengthened in a conventional manner by condensation with acetone in the cold (i.e. at a temperature of about 0°-30° C.) in the presence of alkali (e.g. dilute aqueous sodium hydroxide to give a (R_1-R_5)-phenyl-but-3-en-2-one which can be converted into the corresponding (R_1-R_5)-phenyl-3-methyl-3-hydroxy-penta-4-en-1-yne in a manner known per se by means of an organometallic reaction (e.g. by means of a Grignard reaction by the addition of acetylene). The resulting tertiary ethylenic carbinol can subsequently be partially hydrogenated in a conventional manner using a partially deactivated noble metal catalyst (lindlar catalyst). The resulting tertiary ethylenic carbinol can subsequently be converted, under allyl rearrangement, into the desired phosphonium salt of formula II-b where m stands for 1 by treatment with a triaryl phosphine, especially with triphenyl phosphine, in the presence of a hydrohalide such as hydrogen chloride or hydrogen bromide in a solvent (e.g. in benzene). The tertiary ethylenic carbinol can, moreover, be halogenated to give the compound of formula II where m is 1 and A is a halide, i.e. the compound of formula II-k. This halide of formula II-k can be reacted with a trialkyl phosphite (e.g. triethyl phosphite) to give a corresponding phosphonate of formula II-d.

Compounds of formula II where m is 0 and A is a sulfone group have the formula:



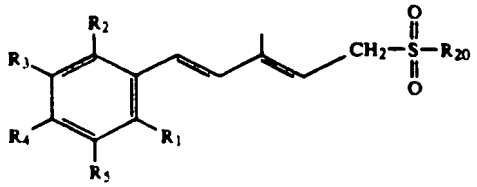
II-e

wherein R_1, R_2, R_3, R_4, R_5 and R_{20} are as above.

Compounds of formula II-e can be prepared, for example, by dissolving a (R_1-R_5)-phenol or a corresponding halobenzene in a polar solvent such as alcohol (e.g. methanol, ethanol or isopropanol) or in tetrahydrofuran or dimethylformamide or in glacial acetic acid and treating the solution at room temperature with a sulfinic acid of the formula:

wherein R_{20} is as above, or with an alkali salt thereof. The sulfone can be isolated, for example, by making the reaction mixture neutral by adding an aqueous sodium hydrogen carbonate solution and extracting the sulfone with an organic solvent (e.g. ethyl acetate or ether).

Compounds of formula II where m is 1 and A is a sulfone group having the formula:



II-f

wherein R_1, R_2, R_3, R_4, R_5 and R_{20} are as above;

Compounds of formula II-f can be prepared in an analogous manner by reacting a (R_1-R_5)-phenyl-3-methyl-penta-2,4-dien-1-ol or a halide thereof with a sulfinic acid as set forth hereinabove or with an alkali salt thereof.

Compounds of formula II where m is zero and A is oxo, i.e., the compound of formula II-g can be prepared, for example, by formylating in the previously described manner a (R_1-R_5)-benzene. In this manner, a (R_1-R_5)-benzaldehyde is directly obtained from the (R_1-R_5) benzene.

Compounds of formula II where m is 1 and A is oxo, i.e., the compound of formula II-h can be prepared, for example, by submitting a (R_1-R_5)-phenyl-but-3-en-2-one, described hereinbefore in connection with the preparation of compounds of formula II-b, to a Wittig reaction with ethoxycarbonyl-methylenetriphenylphosphorane or with diethyl-phosphonoacetic acid ethyl ester. The resulting (R_1-R_5)-phenyl-3-methyl-penta-2,4-dien-1-oic acid ethyl ester is subsequently reduced in the cold with a mixed metal hydride, especially lithium aluminium hydride, in an organic solvent (e.g. diethyl ether or tetrahydrofuran) to give a (R_1-R_5)-phenyl-3-methyl-penta-2,4-dien-1-ol. This alcohol is then oxidized by treatment with an oxidizing agent, for example, with manganese dioxide in an organic solvent such as acetone or methylene chloride at a temperature between 0° C. and the boiling point of the mixture to give the desired (R_1-R_5)-phenyl-3-methyl-penta-2,4-dien-1-al of formula II-h.

The compounds of formula III are also, in part, novel.

Compounds of formula III where n is zero and B is a triarylphosphonium group [III-a] or a dialkoxyphosphinyl group [III-c] can be readily prepared by reacting an optionally esterified 3-halomethyl-crotonic acid or an etherified 3-halomethyl-crotyl alcohol with a triaryl phosphine in a solvent, preferably with triphenyl phosphine in toluene or benzene, or with a trialkyl phosphite, especially with triethyl phosphite.

Compounds of formula III where n is 1 and B is a triarylphosphonium group [III-b] or a dialkoxyphosphinyl group [III-d] can be prepared, for example, by reducing the formyl group of an aldehyde of formula III-h in which n stands for 1 to the hydroxymethyl group using a metal hydride such as sodium borohy-

dride in an alkanol (e.g. ethanol or isopropanol). The resulting alcohol can be halogenated using a conventional halogenating agent (e.g. phosphorus oxychloride) and the resulting 8-halo-3,7-dimethyl-octa-2,4,6-triene-1-carboxylic acid (a halide of formula III in which n stands for 1 and B is halogen) or a derivative thereof can be reacted either with a triaryl phosphine in a solvent, preferably with triphenyl phosphine in toluene or benzene, to give a desired phosphonium salt of formula III-b or with a trialkyl phosphite, especially with triethyl phosphite, to give a desired phosphonate of formula III-d.

Compounds of formula III-e where n is zero and B is a sulfone group can be prepared, for example, by reacting 4-hydroxy-3-methyl-but-2-en-1-al or the corresponding acetate or bromide in a polar solvent (e.g. isopropanol or n-butanol) in the manner previously described with one of the sulfinic acids defined hereinbefore or with an alkali metal salt thereof.

Compounds of formula III-f where n is 1 and B is a sulfone group can be prepared in a manner analogous to that described earlier by the reaction of, for example, 8-hydroxy-3,7-dimethyl-octa-2,4,6-trien-1-oic acid or the corresponding acetate or bromide of this alcohol with a sulfinic acid as hereinbefore defined or with an alkali metal salt thereof.

Compounds of formula III-g where n is zero and B is an oxo group can be prepared, for example, by oxidatively cleaving an optionally esterified tartaric acid; for example, using lead tetraacetate at room temperature in an organic solvent such as benzene. The resulting glyoxalic acid derivative is subsequently condensed in a manner known per se, conveniently in the presence of an amine, with propionaldehyde at an elevated temperature (e.g. at a temperature between 60° C. and 110° C.) with water cleavage to give the desired 3-formyl-crotonic acid derivative.

Compounds of formula III-h where n is 1 and B is an oxo group can be prepared, for example, by reacting 4,4,-dimethoxy-3-methyl-but-1-en-3-ol with phosgene in the cold, preferably at −10° C. to −20° C., in the presence of a tertiary amine such as pyridine and condensing the resulting 2-formyl-4-chloro-but-2-ene under conditions of a Wittig reaction with an optionally esterified 3-formyl-crotonic acid or to an optionally esterified or etherified 3-formyl-crotyl alcohol to give the desired aldehyde of formula III-b.

According to the process provided by the present invention, the following reactions are effected:

phosphonium salts of formula II-a or II-b are reacted with aldehydes of formula III-h or III-g, or

phosponium salts of formula III-a or III-b are reacted with aldehydes of formula II-h or II-g, or

phosphonates of formula II-c or II-d are reacted with aldehydes of formula III-h or III-g, or

phosphonates of formula III-c or III-d are reacted with aldehydes of formula II-h or II-g, or

sulfones of formula II-e or II-f are reacted with halides of formula III-k or III-i, or

sulfones of formula III-e or III-f are reacted with halides of formula II-k or II-i.

According to the Wittig procedure, the reaction components are reacted with one another in the presence of an acid binding agent, for example, in the presence of an alkali metal alcoholate such as sodium methylate or in the presence of an optionally alkyl-substituted alkylene oxide, especially in the presence of

ethylene oxide or 1,2-butylene oxide, if desired in a solvent (e.g. in a chlorinated hydrocarbon such as methylene chloride or in dimethylformamide) at a temperature between room temperature and the boiling point of the reaction mixture.

According to the Horner procedure, the reaction components are reacted with one another with the aid of a base and preferably in the presence of an inert organic solvent; for example, with the aid of sodium hydride in benzene, toluene, dimethylformamide, tetrahydrofuran, dioxan or 1,2-dimethoxyethane or with the aid of an alkali metal alcoholate in an alkanol (e.g. sodium methylate in methanol) at a temperature between 0° C. and the boiling point of the reaction mixture.

According to the Julia procedure, the reaction components are reacted with one another with the aid of a condensation agent, conveniently in the presence of a polar solvent. Suitable solvents are, for example, dimethylformamide, dimethyl sulphoxide, dimethylacetamide, tetrahydrofuran and hexamethylphosphoric acid triamide as well as alkanols such as methanol, isopropanol or tertbutanol. Examples of strong bases which are preferably used as the condensation agent are alkali metal carbonates (especially sodium carbonate), alkaline earth metal carbonates, alkali metal hydroxides (e.g. sodium hydroxide or potassium hydroxide), alkali metal alcoholates (e.g. sodium methylate and, especially, potassium tertbutylate), alkaline earth metal alcoholates, alkali metal hydrites (e.g. sodium hydride), alkyl-magnesium halides (e.g. methyl-magnesium bromide) and alkali metal amides (e.g. sodium amide). The reaction is expediently carried out at a low temperature, especially at a temperature below the freezing point (e.g. between −50° C. and −80° C.).

It has been shown to be convenient in certain cases to carry out the reactions described hereinbefore in situ; i.e. without isolating the phosphonium salt, phosphonate or sulfone from the medium in which it is prepared.

A carboxylic acid of formula I can be converted in a manner known per se (e.g. by treatment with thionyl chloride, preferably in pyridine) into an acid chloride which can be converted by treatment with ammonia into an amide and by reaction with an alkanol into an ester.

A carboxylic acid ester of formula I can be hydrolysed in a manner known per se (e.g. by treatment with an alkali, especially aqueous-alcoholic sodium hydroxide or potassium hydroxide) at a temperature between room temperature and the boiling point of the mixture and then amidated either via an acid halide or as described hereinafter.

A carboxylic acid ester of formula I can be converted directly into a corresponding amide, for example, by treatment with lithium amide. The lithium amide is advantageously treated with the ester at room temperature.

A carboxylic acid or a carboxylic acid ester of formula I can be reduced in a manner known per se to give a corresponding alcohol of formula I. The reduction is advantageously carried out using a metal hydride or alkyl metal hydride in an inert solvent. The preferred hydrides are the mixed metal hydrides such as lithium aluminium hydride or bis[methoxy-ethylenoxy]-sodium aluminium hydride. Suitable solvents are, inter alia, ether, tetrahydrofuran or dioxan when lithium aluminium hydride is used and ether, hexane, benzene or toluene when diisobutyl aluminium hydride or bis[methoxy-ethylenoxy]-sodium aluminium hydride is used.

An alcohol of formula I can be etherified with an alkyl halide (e.g. ethyl iodide), for example, in the presence of a base, preferably sodium hydride, in an organic solvent such as dioxan, tetrahydrofuran, 1,2-dimethoxyethane, dimethylformamide or in the presence of an alkali metal alcoholate in an alkanol at a temperature between 0° C. and room temperature.

An alcohol of formula I can also be esterified by treatment with an alkanoyl halide or anhydride, expediently in the presence of a base (e.g. pyridine or triethylamine) at a temperature between room temperature and the boiling point of the mixture.

An alcohol ester can be saponified in a manner known per se; for example, in the manner previously described in connection with the hydrolysis of a carboxylic acid ester.

An alcohol of formula I or an ester thereof can be oxidized in a manner known per se to give a corresponding acid of formula I. The oxidation is advantageously carried out with silver (I) oxide and alkali in water or in an organic water-miscible solvent at a temperature between room temperature and the boiling point of the mixture.

An amine of formula I forms addition salts with inorganic and organic acids. Examples of such salts are those formed with hydrohalic acids (especially with hydrochloric or hydrobromic acid), with other mineral acids (e.g. with sulphuric acid) and with organic acids (e.g. with benzoic acid, acetic acid, citric acid or lactic acid).

A carboxylic acid of formula I forms salts with bases, especially with alkali metal hydroxides and especially with sodium hydroxide or potassium hydroxide.

The compounds of formula I can occur as cis/trans mixtures which, if desired, can be separated into the cis and trans components or isomerised to the all-trans compounds in a manner known per se.

The following examples are illustrative but not limitative of this invention. In the examples, the ether utilized was diethyl ether. In the examples concentrated hydrochloric acid denotes an aqueous solution containing about 37% by weight hydrochloric acid. The term 35% formaldehyde which appears in the Examples indicates an aqueous solution containing 35% formaldehyde. The term "low boiling petroleum ether" as used in the examples designates petroleum ether boiling at °C.

The sodium hydride (50–60%) utilized in the examples refers to a mineral oil suspension containing 30 to 60% by weight sodium hydride.

EXAMPLE 1

228 g of 5-(4-methoxy-2,3,6-trimethyl-phenyl)-3-methyl-penta-2,4-diene-1-triphenylphosphonium bromide are introduced under nitrogen gassing into 910 ml of dimethylformamide and treated with cooling at 5°–10° C. within 20 minutes with 17.5 g of a suspension of sodium hydride (about 50% by weight) in mineral oil. The mixture is stirred for 1 hour at about 10° C., then treated at 5°–8° C. dropwise with 61.8 g of 3-formylcrotonic acid butyl ester, heated for 2 hours at 65° C., subsequently introduced into 8 l of ice-water and, after the addition of 300 g of sodium chloride, thoroughly extracted with a total of 18 l of hexane. The extract is washed 5 times with 1 l of methanol/water (6:4 parts by volume) each time and 2 times with 1.5 l of water each time, dried over sodium sulphate and evaporated under reduced pressure to leave 9-(4-methoxy-2,3,6-trimethyl-

phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester, m.p. 80°–81° C. as the residue.

EXAMPLE 2

125.8 g of 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester are introduced into 2000 ml of abs. ethanol and treated with a solution of 125.8 g of potassium hydroxide in 195 ml of water. The mixture is heated to boiling under nitrogen gassing for 30 minutes, then cooled, introduced into 10 l of ice-water and, after the addition of about 240 ml of conc. hydrochloric acid [pH 2–4], thoroughly extracted with a total of 9 l of methylene chloride. The extract is washed with about 6 l of water to neutrality, dried over calcium chloride and evaporated under reduced pressure. The residue is taken up in 700 ml of hexane. The precipitated 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid melts at 228°–230° C.

EXAMPLE 3

500 g of 2,3,5-trimethylphenol are introduced into 1840 ml of ethanol and 184 ml of water and treated, with gentle stirring, with 240 g of potassium hydroxide. To the resulting clear solution, there are added dropwise at 0°–5° C. within 30–45 minutes 626 g of methyl iodide. The reaction mixture is stirred for 2 hours at room temperature, subsequently stirred under reflux conditions for 12 hours at 60° C., then treated with 5 l of water and thoroughly extracted with a total of 6 l of diethyl ether. The extract is washed first with 3 l of 3 aqueous sodium hydroxide, then washed 2 times with 1 l of water each time, dried over sodium sulphate and evaporated under reduced pressure. The remaining 2,3,5-trimethylanisole, after rectification, boils at 88°–90° C./10 mm Hg.

184 g of phosphorus oxychloride are added dropwise to 87.1 g of dimethylformamide with stirring at 10°–20° C. within 20–30 minutes. The temperature should rise to 25° C. towards the end of the addition. Into the obtained mixture, there are introduced 150 g of 2,3,5-trimethylanisole within 20 minutes with cooling at 10°–20° C. The reaction mixture is slowly heated up to max. 115° C., stirred for 6 hours at 100° C. for the completion of the reaction, poured, after cooling, into 2 kg of ice/water 1:1 parts by volume and, after the addition of 1500 ml of benzene, treated with 500 g of sodium acetate. The water phase which forms is separated after stirring for 1 hour and again extracted with 1000 ml of benzene. The combined benzene extracts are washed successively with 480 ml of 1.5 aqueous hydrochloric acid and 500 ml of water, dried over sodium sulphate and filtered over 20 g of decoloring carbon. The filtrate is evaporated under reduced pressure. The remaining 2,3,6-trimethyl-p-anisaldehyde melts, after recrystallisation from hexane, at 65°–66° C.

260 g of 2,3,6-trimethyl-p-anisaldehyde are introduced into a mixture of 3500 ml of acetone and 1400 ml of water and treated with 730 ml of 10 wt.% aqueous sodium hydroxide with stirring at 0°–5° C. in the course of about 30 minutes. The mixture is stirred for 3 days at room temperature and subsequently, after lowering of the pH value to 4–5 by addition of acetic acid, concentrated under reduced pressure. The concentrate is extracted with a total of 3000 ml of diethyl ether. The ether extract is washed first with 700 ml of an aqueous 5% by weight sodium bicarbonate solution, then washed with 700 ml of water, dried over sodium sul-

phate and evaporated under reduced pressure. The remaining oily 4-(4-methoxy-2,3,6-trimethyl-phenyl)-but-3-en-2-one boils, after rectification, at 120°–127° C./0.05 mm Hg.

36.45 g of magnesium are superficially corroded with a small amount of iodine, introduced into 1000 ml of tetrahydrofuran and treated dropwise with 162.5 g of ethyl bromide under nitrogen within 45 minutes. In so doing, the temperature should amount initially to 8°–10° C. It can rise to 25° C. towards the end of the introduction. The reaction mixture is stirred, optionally with renewed addition of a further 5–10 ml of alkyl bromide, until the magnesium has gone completely into solution. The obtained Grignard solution is subsequently added dropwise at 0° C. into a saturated acetylene/tetrahydrofuran solution manufactured from 650 ml of tetrahydrofuran by gassing for 3 hours with acetylene at −10° to −5° C. The reagent is stirred for 1 hour at 0° C., then treated dropwise within 30–45 minutes with acetylene gassing at 0° C., with a solution of 218 g of 4-(4-methoxy-2,3,6-trimethyl-phenyl)-but-3-en-2-one in 250 ml of tetrahydrofuran. The reaction mixture is stirred for 24 hours at 0° C. and subsequently for 12 hours at room temperature, then introduced into 4.5 kg of ice/-water 3.5:1 parts by volume, adjusted to a pH of about 4 by the addition of 700 ml of 3 N hydrochloric acid and thoroughly extracted with a total of 3 l of diethyl ether. The ether extract is washed to neutrality with a total of 2 l of water, dried over sodium sulphate and filtered over 20 g of decoloring carbon. The filtrate is evaporated under reduced pressure, the remaining 5-(4-methoxy-2,3,6-trimethyl-phenyl)-3-methyl-3-hydroxy-penta-4-en-1-yne, after rectification at 125°–135° C./0.04 mm Hg, melts at 58°–60° C.

244 g of 5-(4-methoxy-2,3,6-trimethyl-phenyl)-3-methyl-3-hydroxy-penta-4-en-1-yne are dissolved in 400 ml of hexane and, after the addition of 45 g of a partially poisoned palladium catalyst, hydrogenated at room temperature under normal pressure. The hydrogenation is stopped after about 40–60 minutes after the uptake of the amount of hydrogen necessary for the saturation of the acetylene-ethylene bond [25 l]. The hydrogenation solution is filtered. The filtrate is washed with 300 ml of ethyl acetate and evaporated under reduced pressure. The remainin 5-(4-methoxy-2,3,6-trimethyl-phenyl)-3-methyl-3-hydroxy-pent-1,4-diene melts at 46°–47° C.

246 g of 5-(4-methoxy-2,3,6-trimethyl-phenyl)-3-methyl-3-hydroxy-penta-1,4-diene are dissolved in 2400 ml of benzene. The solution is treated with 343 g of triphenylphosphonium hydrobromide, stirred for 24 hours at 60° C., then cooled and the benzene separated. The sediment is digested 4 times with 500 ml of benzene each time and, after separation of the benzene washings, dissolved in 700 ml of methylene chloride. The solution is evaporated under reduced pressure. The remaining 5-(-4-methoxy-2,3,6-trimethyl-phenyl)-3-methyl-penta-2,4-diene-1-triphenylphosphonium bromide is dried in vacuo before further processing.

EXAMPLE 4

1775 g of lead tetraacetate (90%) are gradually introduced within 30 minutes at 25°–30° C. into a solution of 1000 g of L(+)-tartaric acid dibutyl ester in 3850 ml of benzene. The reaction mixture is subsequently stirred for 1 hour at room temperature. The sediment is filtered off and extracted with 500 ml of benzene. The benzene extract is evaporated under reduced pressure. The re-

maining glyoxalic acid butyl ester boils, after rectification, at 50°-65° C./12 mm Hg.

836 g of the obtained glyoxalic acid butyl ester are introduced into 376 g of propionaldehyde. The mixture is treated dropwise at 60° C. with 40.8 g of di-n-butylamine. In so doing, the reaction temperature should not rise higher than 106° C. The reaction mixture is then stirred for 2 hours at 116°-111° C., cooled and taken up in ether. The diethyl ether extract is washed successively with 500 ml of 1 N sulphuric acid, 700 ml of water, 1000 ml of 5% by weight aqueous sodium bicarbonate solution and subsequently with 1000 ml of water, dried over sodium sulphate and evaporated under reduced pressure. The remaining 3-formyl-crotonic acid butyl ester boils, after rectification, at 93°-105° C./14 mm Hg; $n_D^{25} = 1$

EXAMPLE 5

28.5 g of 5-(4-methoxy-2,3,6-trimethyl-phenyl)-3-methyl-penta-2,4-diene-1-triphenylphosphonium bromide are introduced under nitrogen gassing into 240 ml of isopropyl alcohol. After the addition of 0.12 g of butylated hydroxy toluene, the mixture is cooled to −35° C. and treated at this temperature under strong stirring within 5 minutes with 7.50 g of 3-formylcrotyl acetate. The reaction mixture is subsequently mixed with 7.2 g of a 50 wt.% aqueous potassium hydroxide solution—in so doing the temperature should not rise above −25° C.—and, after stirring for 1 hour at −30° C., introduced into a mixture of 110 g of water, 90 g of ice and 90 ml of hexane. The hexane layer is separated. The aqueous phase is shaken out 5 times with 90 ml of hexane each time. The combined hexane extracts are shaken out 5 times with 180 ml of methanol/water 80:20 parts by volume each time. The hexane phase is washed with water, dried over sodium sulphate and evaporated under reduced pressure. The remaining 1-acetoxy-9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraene, an oil, can be purified by absorption on silica gel eluent: hexane/diethyl ether 80:20 parts by volume.

EXAMPLE 6

59 g of 2,3,6-trimethyl-benzyl-triphenylphosphonium bromide and 28 g of 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester are introduced into 280 ml of abs. ethanol. The mixture is treated dropwise at a temperature between 0° and 10° C. with a solution of 2.72 g of sodium in 160 ml of abs. ethanol, subsequently stirred for 48 hours at room temperature, then introduced into 800 ml of water and thoroughly extracted with a total of 3000 ml of hexane. The hexane extract is shaken out 3 times with 1000 ml of methanol/water 60:40 parts by volume each time, then dried over sodium sulphate and evaporated under reduced pressure. The remaining 9-(2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester is an oil.

EXAMPLE 7

10 g of 9-(2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester are introduced into 100 ml of abs. ethanol and, after the addition of a solution of 10 g of potassium hydroxide in 20 ml of water, heated to boiling under nitrogen gassing. The initially cloudy solution becoming clear when boiling is cooled after 30 minutes and introduced into ice-water. The reaction solution is thoroughly extracted, after acidification with conc. hydrochloric acid, with methylene

chloride. The extract is washed to neutrality with water, dried over calcium chloride and evaporated under reduced pressure. The remaining 9-(2,3,6-trimethylphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid melts, after recrystallisation from ethyl acetate, at 191°-192° C.

EXAMPLE 8

300 g of pseudocumol are treated dropwise with 700 ml of conc. sulphuric acid. In so doing, the temperature can rise to 40° C. The mixture is subsequently cooled to 20° C. and, after the addition of 450 g of bromine, stirred for 1 hour at room temperature. Thereafter, 700 ml of water are added dropwise. In so doing, the temperature rises to 50° C. The precipitated mixture of solid materials is filtered off and dissolved in 3000 ml of hot water. The insoluble 3,5,6-tribromo-1,2,4-trimethylbenzene is separated and rejected. The aqueous solution is slowly introduced into 1000 ml of 80 wt.% sulphuric acid which is being heated at 180° C. and blown through with steam. The 1-bromo-2,3,6-trimethylbenzene coming over with the steam boils at 86° C./6 mm Hg.

250 g of 1-bromo-2,3,6-trimethylbenzene are dissolved in 400 ml of diethyl ether. The solution is added dropwise at 20°-30° C. with gentle cooling into a suspension of 66.5 g of magnesium (activated with iodine) and 200 ml of diethyl ether. The mixture is treated dropwise at 20°-30° C. with a solution of 135 g of ethyl bromide in 250 ml of diethyl ether and subsequently heated to boiling under reflux conditions for 3–4 hours. As soon as the magnesium has gone into solution, 385 g of orthoformic acid ethyl ester dissolved in 250 ml of abs. diethyl ether are introduced. The reaction mixture is heated to boiling for 5 hours, after evaporation of the diethyl ether poured onto ice, treated with 1000 ml of 5 N hydrochloric acid and heated to boiling for 30 minutes under carbon dioxide gassing. The distillate, obtainable thereafter by water distillation, is extracted with methylene chloride. The methylene chloride phase is evaporated under reduced pressure. The remaining 2,3,6-trimethylbenzaldehyde boils at 70°-72° C./1.2 mm Hg.

129.6 g of 2,3,6-trimethylbenzaldehyde are dissolved in 300 ml of methanol and, after the addition of 70 ml of water, cooled to 0°. The mixture is treated portion-wise with 18.25 g of sodium borohydride, stirred for 1 hour, subsequently poured onto ice and thoroughly extracted with diethyl ether. The ether extract is dried over sodium sulphate and evaporated under reduced pressure. The remaining 2,3,6-trimethylbenzyl alcohol is further processed as follows:

75 g of 2,3,6-trimethylbenzyl alcohol are dissolved in 175 ml of low-boiling petroleum ether. The solution is treated dropwise within 2 hours at −10° C. with a solution of 51 g of phosphorus tribromide in 60 ml of low-boiling petroleum ether. The reaction mixture is stirred for 12 hours at room temperature, then poured onto ice and extracted with diethyl ether. The ether extract is washed first with an ice-cold, saturated, aqueous sodium bicarbonate solution, then with a saturated aqueous common salt solution, dried over sodium sulphate and evaporated under reduced pressure. The remaining 2,3,6-trimethylbenzyl bromide boils, after rectification, at 75°-80° C./0.05 mm Hg.

73.3 g of 2,3,6-trimethylbenzyl bromide are dissolved in 170 ml of benzene. The solution is treated with 90.0 g of triphenyl phosphine. In so doing, the temperature rises to 40° C. The mixture is stirred for 12 hours at

chloride. The extract is washed to neutrality with water, dried over calcium chloride and evaporated under reduced pressure. The remaining 9-(2,3,6-trimethylphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid melts, after recrystallisation from ethyl acetate, at 191°-192° C.

EXAMPLE 8

300 g of pseudocumol are treated dropwise with 700 ml of conc. sulphuric acid. In so doing, the temperature can rise to 40° C. The mixture is subsequently cooled to 20° C. and, after the addition of 450 g of bromine, stirred for 1 hour at room temperature. Thereafter, 700 ml of water are added dropwise. In so doing, the temperature rises to 50° C. The precipitated mixture of solid materials is filtered off and dissolved in 3000 ml of hot water. The insoluble 3,5,6-tribromo-1,2,4-trimethylbenzene is separated and rejected. The aqueous solution is slowly introduced into 1000 ml of 80 wt.% sulphuric acid which is being heated at 180° C. and blown through with steam. The 1-bromo-2,3,6-trimethylbenzene coming over with the steam boils at 86° C./6 mm Hg.

250 g of 1-bromo-2,3,6-trimethylbenzene are dissolved in 400 ml of diethyl ether. The solution is added dropwise at 20°-30° C. with gentle cooling into a suspension of 66.5 g of magnesium (activated with iodine) and 200 ml of diethyl ether. The mixture is treated dropwise at 20°-30° C. with a solution of 135 g of ethyl bromide in 250 ml of diethyl ether and subsequently heated to boiling under reflux conditions for 3–4 hours. As soon as the magnesium has gone into solution, 385 g of orthoformic acid ethyl ester dissolved in 250 ml of abs. diethyl ether are introduced. The reaction mixture is heated to boiling for 5 hours, after evaporation of the diethyl ether poured onto ice, treated with 1000 ml of 5 N hydrochloric acid and heated to boiling for 30 minutes under carbon dioxide gassing. The distillate, obtainable thereafter by water distillation, is extracted with methylene chloride. The methylene chloride phase is evaporated under reduced pressure. The remaining 2,3,6-trimethylbenzaldehyde boils at 70°-72° C./1.2 mm Hg.

129.6 g of 2,3,6-trimethylbenzaldehyde are dissolved in 300 ml of methanol and, after the addition of 70 ml of water, cooled to 0°. The mixture is treated portion-wise with 18.25 g of sodium borohydride, stirred for 1 hour, subsequently poured onto ice and thoroughly extracted with diethyl ether. The ether extract is dried over sodium sulphate and evaporated under reduced pressure. The remaining 2,3,6-trimethylbenzyl alcohol is further processed as follows:

75 g of 2,3,6-trimethylbenzyl alcohol are dissolved in 175 ml of low-boiling petroleum ether. The solution is treated dropwise within 2 hours at −10° C. with a solution of 51 g of phosphorus tribromide in 60 ml of low-boiling petroleum ether. The reaction mixture is stirred for 12 hours at room temperature, then poured onto ice and extracted with diethyl ether. The ether extract is washed first with an ice-cold, saturated, aqueous sodium bicarbonate solution, then with a saturated aqueous common salt solution, dried over sodium sulphate and evaporated under reduced pressure. The remaining 2,3,6-trimethylbenzyl bromide boils, after rectification, at 75°-80° C./0.05 mm Hg.

73.3 g of 2,3,6-trimethylbenzyl bromide are dissolved in 170 ml of benzene. The solution is treated with 90.0 g of triphenyl phosphine. In so doing, the temperature rises to 40° C. The mixture is stirred for 12 hours at

room temperature. The precipitated 2,3,6-trimethylbenzyl-triphenylphosphonium bromide melts, after washing with low-boiling petroleum ether and drying, at 240°-242° C.

EXAMPLE 9

After the addition of a slight amount of iron (III) nitrate, 2700 ml of liquid ammonia are treated portionwise with stirring and cooling with 169.5 g of potassium. As soon as the initially blue coloration has disappeared, i.e. after about 30–45 minutes, acetylene gas in a stream of 3 l/min. is led in until the dark coloration of the reaction mixture becomes lighter. Then, the gas stream is reduced to 2 l/min. and the mixture treated dropwise with a solution of 500 g of methylglyoxal-dimethylacetal in 425 ml of abs. diethyl ether. The gassing with acetylene is continued for 1 hour with stirring. The reaction mixture is subsequently treated portionwise with 425 g of ammonium chloride, gradually warmed to 30° C. within 12 hour with evaporation of the ammonia and extracted with 1600 ml of diethyl ether. The ether extract is dried over sodium sulphate and evaporated under reduced pressure. The remaining 4,4-dimethoxy-3-methylbut-1-yn-3-ol boils, after rectification, at 33° C./0.03 mm Hg; $n_D^{25} = 1.4480$.

198 g of 4,4-dimethoxy-3-methyl-but-1-yn-3 -ol are dissolved in 960 ml of high-boiling petroleum ether and, after the addition of 19.3 5% palladium catalyst and 19.3 g of quinoline, hydrogenated under normal conditions. After the uptake of 33.5 l of hydrogen, the hydrogenation is stopped. The catalyst is filtered off. The filtrate is evaporated under reduced pressure. The remaining 4,4-dimethoxy-3-methyl-but-1-en-3-ol boils, after rectification, at 70°-72° C./18 mm Hg.

195 ml of phosgene are led into 1570 ml of carbon tetrachloride at −10° C. After the addition of 213 g of pyridine, the solution is treated dropwise at a temperature of −10° to −20° C. with 327 4,4-dimethoxy-3-methyl-but-1-en-3-ol. The reaction mixture is slowly warmed to 25° C. with stirring, stirred for a further 3 hours at room temperature, cooled to 15° C. and treated with 895 ml of water. The aqueous phase is separated and rejected. The organic phase is treated, after standing for 12 hours in the cold, with 448 ml of 5% by weight aqueous sulphuric acid, stirred for 5 hours, then washed with water, dried over sodium sulphate and evaporated under reduced pressure. The remaining 2-formyl-4-chloro-but-2-ene boils, after rectification, at 37°–40° C./1.8 mm Hg; $n_D^{25} = 1.4895$.

165.7 g of 2-formyl-4-chloro-but-2-ene are dissolved in 840 ml of benzene and treated with 367 g of triphenyl phosphine. The reaction mixture is heated to boiling under reflux conditions for 12 hours with nitrogen gassing, then cooled to 20° C. The precipitated 2-formyl-but-2-ene-4-triphenyl-phosphonium chloride melts, after washing with benzene and drying, t 250°-252° C.

212.6 g of 2-formyl-but-2-ene-4-triphenylphosphonium chloride and 95 g of 3-formylcrotonic acid butyl ester are introduced into 1100 ml of butanol and treated at 5° C. with a solution of 57 g of triethylamine in 60 ml of butanol. The reaction mixture is subsequently stirred for 6 hours at 25° C., then cooled and introduced into water and thoroughly extracted with hexane. The hexane phase is washed first repeatedly with methanol/water (6:4 parts by volume), then with water, dried over sodium sulphate and filtered. The filtrate is isomerised for 12 hours by shaking with iodine. The iodine is removed by the addition of sodium

thiosulphate. The filtrate is washed again with water, dried and evaporated under reduced pressure. The remaining 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester boils, after rectification, at 102°–105° C./0.09 mm Hg.

EXAMPLE 10

By the procedure of Example 6:

2,4,6-triisopropyl-benzyl-triphenylphosphonium bromide is condensed with

7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester to form

9-(2,4,6-triisopropyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester (oil);

which is hydrolyzed by the procedure of Example 7 to form:

9-(2,4,6-triisopropyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid m.p.: 221° C.

EXAMPLE 11

136 g of 1,3,5-triisopropyl-benzene, 228 ml of acetic acid, 420 ml of conc. hydrochloric acid and 55 g of formaldehyde (35%) are heated to 60° C. The reaction mixture is stirred at this temperature firstly for 3 hours, then, after the renewed addition of 21 g of formaldehyde (35%), for a further 12 hours, then cooled to room temperature and thoroughly extracted with benzene. The benzene extract is washed successively with water, with a saturated aqueous sodium bicarbonate solution and again with water, dried over sodium sulphate and evaporated under reduced pressure. The remaining 2,4,6-triisopropyl-benzyl chloride boils, after rectification, at 70° C./0.05 mm Hg.

69.6 g of 2,4,6-triisopropyl-benzyl chloride are dissolved in 1000 ml of xylene. The solution is treated with 79.5 g of triphenyl phosphine. The mixture is stirred for 18 hours at 125° C., then cooled. The 2,4,6-triisopropyl-benzyl-triphenylphosphonium chloride already precipitated at 80° C. melts, after trituration and washing with benzene, at 237°–238° C.

EXAMPLE 12

By the procedure of Example 6:

pentamethyl-benzyl-triphenylphosphonium chloride is condensed with

7-formyl-3-methyl-octa-2,4,6-trien-1-oic-acid butyl ester to produce

9-(pentamethyl-phenyl)-3,7-dimethyl-nona,2,4,6,8-tetraen-1-oic acid butyl ester (oil);

which is hydrolyzed by the procedure of Example 7 to the

9-(pentamethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic-acid m.p.: 228°–229° C.

EXAMPLE 13

184.5 g of pentamethylbenzene, 193 ml of glacial acetic acid, 355 ml of conc. hydrochloric acid and 44 g of formaldehyde (35%) are heated to 65° C. The reaction mixture is stirred at this temperature first for 3 hours, then, after the renewed addition of 18.1 g of formaldehyde (35%) for a further 3 hours, then cooled to room temperature and thoroughly extracted for a further 12 hours with benzene. The benzene extract is washed successively with water, diluted aqueous sodium hydroxide and water, dried over sodium sulphate and evaporated under reduced pressure. The remaining pentamethyl-benzyl chloride melts, after recrystallisation from hexane, at 80°–81° C.

101.6 g of pentamethyl-benzyl chloride, 149 g of triphenyl phosphine and 250 ml of toluene are stirred for 5 hours at 100° C. The pentamethyl-benzyl-triphenylphosphonium chloride precipitated with cooling of the reaction mixture, melts, after trituration and washing with low-boiling petroleum ether, at 258°–259° C.

EXAMPLE 14

16 g of 3-chloro-2,4,6-trimethyl-benzyl-triphenylphosphonium chloride and 10 g of 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester are heated to boiling with stirring after the addition of 40 g of 1,2-butylene oxide. The 1,2-butylene oxide is slowly distilled off. The reaction mixture is stirred for 30 minutes at 80°–82° C., then cooled and thoroughly extracted with hexane. The hexane extract is shaken out 5 times with 50 ml of methanol/water 70:30 parts by volume each time, then dried over sodium sulphate and evaporated under reduced pressure to produce 9-(3-chloro-2,4,6-trimethyl-phenyl), 3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester as a residue.

EXAMPLE 15

5 g of 9-(3-chloro-2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester are heated to boiling under nitrogen gassing in 50 ml of a 5% by weight ethanolic potassium hydroxide solution. The solution becoming clear with boiling is cooled after 30 minutes, introduced into water and made acidic by the addition of the acetic acid. The precipitated 9-(3-chloro-2,4-6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid melts, after recrystallization from benzene, at 208°–209° C.

EXAMPLE 16

119 g of chloromesitylene, 11.9 g of paraformaldehyde and 5.95 g of zinc chloride (anhydrous) are heated to 60° C. and gassed with hydrogen chloride, with stirring, firstly for 8 hours and, after the addition of a further 11.9 g of paraformaldehyde, for a further 8 hours. The reaction mixture is then poured onto ice and thoroughly extracted with diethyl ether. The ether extract is washed successively with water, with a saturated aqueous sodium bicarbonate solution and with water, dried over sodium sulphate and evaporated. The remaining 3-chloro-2,4,6-trimethyl-benzyl chloride boils, after rectification, at 138° C./17 mm Hg.

71.25 g of 3-chloro-2,4,6-trimethyl-benzyl chloride, 92 g of triphenyl phosphine and 375 ml of abs. toluene are heated at 100° C. for 12 hours. The 3-chloro-2,4,6-trimethyl-benzyl-triphenylphosphonium chloride precipitated with cooling melts at 233°–235° C.

EXAMPLE 17

By the procedure given in Example 14
3-nitro-2,4,6-trimethyl-benzyl-triphenylphosphonium chloride is condensed with
7-formyl-3-methyl-hepta-2,4,6-trien-1-oic acid butyl ester to form
9-(3-nitro-2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester (oil);
which is converted by the procedure of Example 15 to:
9-(3-nitro-2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid, m.p. 205°–206° C.

EXAMPLE 18

10 g of nitromesitylene, 2 g of p-formaldehyde and 1 g of zinc chloride (anhydrous) are heated to 60° C. and gassed with hydrogen chloride for 16 hours with stirring. The reaction mixture is then poured onto ice and thoroughly extracted with diethyl ether. The ether extract is washed successively with water, a saturated, aqueous sodium bicarbonate solution and with water, dried over sodium sulphate and evaporated. The remaining 3-nitro-2,4,6-trimethyl-benzyl chloride, an oil, $n_D^{22} = 1.5373$, is further processed as follows.

11.6 g of 3-nitro-2,4,6-triphenyl-benzyl chloride, 14 g of triphenyl phosphine and 100 ml of abs. benzene are heated to boiling under reflux conditions for 24 hours. The 3-nitro-2,4,6-trimethyl-benzyl-triphenylphosphonium chloride precipitated with cooling melts at 252°–253° C.

EXAMPLE 19

By the procedure of Example 14:

4-methoxy-2,3,5,6-tetramethyl-benzyl-triphenylphosphonium chloride is condensed with

7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester to form:

9-(4-methoxy-2,3,5,6-tetramethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester (oil); which is converted by the procedure of Example 15 to:

9-(4-methoxy-2,3,5,6-tetramethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid, m.p. 230°–233° C.

EXAMPLE 20

15 g of 2,3,5,6-tetramethylphenol are dissolved in 55.3 ml of methanol and, after the addition of 7.25 g of potassium hydroxide in 5.5 ml of water, treated dropwise at 0°–5° C. with 18.8 g of methyl iodide. The reaction mixture is stirred for 2 hours at room temperature and subsequently for 12 hours at 60° C., then cooled, diluted with 150 ml of water and extracted with 100 ml of diethyl ether. The ether extract is washed successively with 3 N sodium hydroxide and water, dried over sodium sulphate and evaporated under reduced pressure. The remaining 2,3,5,6-tetramethylanisole melts, after purification by absorption on silica gel (eluent: methylene chloride), at 53°–55° C.

43 g of 2,3,5,6-tetramethylanisole in 110 ml of acetic acid anhydrous are introduced into 203 ml of 37% by weight aqueous hydrochloric acid and treated dropwise with 21.6 g of 37% formaldehyde. The reaction mixture is heated to 70° C. for 3 hours with stirring and, after the renewed addition of 8.3 g of 37% formaldehyde, stirred for a further 3 hours at 70° C. The mixture is subsequently cooled to room temperature and extracted with 500 ml of benzene. The benzene extract is separated. The aqueous phase is shaken out with benzene. The combined benzene extracts are washed successively with water, with a saturated, aqueous sodium carbonate solution and again with water, dried and evaporated under reduced pressure. The remaining 4-methoxy-2,3,5,6-tetramethyl-benzyl chloride melts, after recrystallisation from ethyl acetate/hexane (1:3 parts by volume) at 104°–105° C.

28 g of 4-methoxy-2,3,5,6-tetramethyl-benzyl chloride, 34.7 g of triphenyl phosphine and 153 ml of toluene are heated at 100° C. for 12 hours. The 4-methoxy-2,3,5,6-tetramethyl-benzyl-triphenylphosphonium chloride precipitated with cooling melts at 251°–252° C.

EXAMPLE 21

60 g of 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid are dissolved in 1000 ml of acetone. After the addition of 128 g of methyl iodide and 128 g of potassium carbonate, the solution is stirred under nitrogen gassing for 16 hours at 55°–60° C. and subsequently evaporated under reduced pressure. The residue is dissolved in 1300 ml of petroleum ether (boiling point 80°–105° C.). The 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid methyl ester crystallising out at −20° C., melts at 98°–99° C.

EXAMPLE 22

By the procedure of Example 21:

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid and ethyl iodide is converted to

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester; m.p.: 104°–105° C.;

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid and isopropyl iodide is converted to

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid isopropyl ester; (oil).

EXAMPLE 23

28.6 g of 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid are introduced into 300 ml of benzene and treated under nitrogen gassing with 12 g of phosphorus trichloride. The benzene is subsequently distilled off under reduced pressure. The remaining 9-(4-methoxy-2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona,2,4,6,8-tetraen-1-oic acid chloride is dissolved in 1200 ml of diethyl ether. The solution is added dropwise at −33° C. into 500 ml of liquid ammonia and stirred for 3 hours. The reaction mixture is then diluted with 500 ml of diethyl ether and stirred without cooling for a further 12 hours, the ammonia evaporating. The residue is dissolved in 10 l of methylene chloride. The solution is washed 2 times with 3 l of water, dried over sodium sulphate and evaporated under reduced pressure. The remaining 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid amide melts, after recrystallisation from ethanol, at 207°–209° C.

EXAMPLE 24

By the procedure of Example 23:

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid chloride and ethylamine are converted to

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl amide; m.p. 179°–180° C.; and

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid chloride and diethylamine are converted to

9-(4-methoxy-2,3,6,-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid diethyl amide; m.p. 105°–106° C.

EXAMPLE 25

Manufacture of a capsule filling material of the following composition:

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester	0.1	g
Wax mixture	51.4	g
Vegetable Oil	103.0	g
Trisodium salt of ethylenediamine tetraacetic acid	0.5	g
Individual weight of a capsule	150	mg
Active material content of a capsule	10	mg

EXAMPLE 26

Manufacture of an ointment containing 0.3% active material of the following composition:

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid	0.3 g
Cetyl alcohol	2.7 g
Lanoline	6.0 g
White Vaseline	15.0 g
Dist. water q.s. ad	100.0 g

EXAMPLE 27

Manufacture of a water/fat emulsion containing 0.3% active material of the following composition:

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl amide	0.3 g
Magnesium stearate	2.0 g
Perhydrosqualene	13.0 g

EXAMPLE 28

Manufacture of a solution containing 0.1% active material of the following composition:

9-(4-Methoxy-2,3,6-trimethyl-phenyl)-3,7-trimethyl-nona-2,4,6,8-tetraen-1-oic acid	0.1	g
Dimethyl sulphoxide	70.0	g
Water q.s. ad	100	ml

EXAMPLE 29

By the procedure of Example 1 9-(4-allyloxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester is manufactured from 5-(4-allyloxy-2,3,6-trimethyl-phenyl)-3-methyl-penta-2,4-diene-1-triphenylphosphonium bromide by reaction with 3-formyl-crotonic acid ethyl ester. This product is converted to 9-(4-allyloxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid of melting point 198°–200° C. by the procedure of Example 2.

The 5-(4-allyloxy-2,3,6-trimethyl-phenyl)-3-methyl-penta-2,4-diene-1-triphenylphosphonium bromide employed as the starting material can be prepared by the procedure of Example 3. This procedure is carried out by alkylation of 1,3,5-trimethylphenol with allyl bromide to give 1,3,5-trimethyl-phenyl allyl ether (boiling point 76°–80° C./0.05 mmHg), by formylation of the ether obtained to give 4-allyloxy-2,3,6-trimethyl-benzaldehyde (boiling point 90°–102° C./0.15 mmHg), by condensation of the aldehyde obtained with acetone to

give 4-(4-allyloxy-2,3,6-trimethyl-phenyl)-but-3-en-1-al (boiling point 135°–138° C./0.05 mmHg), by reaction of the ketone obtained with acetylene to give 5-(4-allyloxy-2,3,6-trimethyl-phenyl)-3-methyl-3-hydroxy-penta-4-en-1-yne, by partial hydrogenation of the tertiary acetylene carbinol obtained to give 5-(4-allyloxy-2,3,6-trimethyl-phenyl)-3-methyl-3-hydroxy-penta-1,4-diene and by reaction of the tertiary ethylene carbinol obtained with triphenylphosphine hydrobromide. There is obtained 5-(4-allyloxy-2,3,6-trimethyl-phenyl)-3-methyl-penta-2,4-diene-triphenylphosphonium bromide which melts at 114°–116° C.

EXAMPLE 30

By the procedure of Example 14, 9-(2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester is manufactured from 2,4,6-trimethyl-benzyl-triphenylphosphonium chloride by reaction with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester. This product is converted to 9-(2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid of melting point 214°–215° C. by the procedure of Example 15.

The 2,4,6-trimethyl-benzyl-triphenylphosphonium chloride employed as the starting material is prepared by the procedure described in Example 18 by haloformylation of mesitylene to give 2,4,6-trimethyl-benzyl chloride (boiling point 112° C./12 mm Hg) and reaction of the latter compound with triphenylphosphine.

EXAMPLE 31

By the procedure of Example 14, 9-(2,3,4,6-tetramethylphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester is manufactured from 2,3,4,6-tetramethyl-benzyltriphenylphosphonium chloride by reaction with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester. From this product, there is produced by the procedure of Example 15 9-(2,3,4,6-tetra-methyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid of melting point 201°–202° C.

The 2,3,4,6-tetramethyl-benzyl-triphenylphosphonium chloride employed as the starting material is prepared by the procedure described in Example 16 by haloformylation of 1,2,3,5-tetramethyl-benzene to give 2,3,4,6-tetramethylbenzyl chloride ($n_D^{20}=1.5571$) and reaction of the latter compound with triphenylphosphine.

EXAMPLE 32

By the procedure described in Example 14, 9-(4-methoxy-2,6-dimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester is manufactured from 4-methoxy-2,6-dimethylbenzyl-triphenylphosphonium chloride by reaction with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester. From this product, there is produced by the procedure of Example 15, 9-(4-methoxy-2,6-dimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid of melting point 207°–208° C.

The 4-methoxy-2,6-dimethyl-benzyl-triphenylphosphonium chloride employed as the starting material is prepared by the procedure described in Example 16 by haloformylation of 3,5-dimethylanisole to give 4-methoxy-2,6-dimethyl-benzyl chloride ($n_D^{20}=1.5475$) and reaction of the latter compound with triphenylphosphine.

EXAMPLE 33

By the procedure described in Example 14, 9-(3-methoxy-2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-

2,4,6,8-tetraen-1-oic acid butyl ester is manufactured from 3-methoxy-2,4,6-trimethyl-benzyl-triphenylphosphonium chloride by reaction with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester. This product is converted to 9-(3-methoxy-2,4,6-trimethylphenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid of melting point 196°-198° C., utilizing the procedure described in Example 15.

The 3-methoxy-2,4,6-trimethyl-benzyl-triphenylphosphonium chloride employed as the starting material is prepared by the procedure described in Example 16 by haloformylation of 2,4,6-trimethylanisole to give 3-methoxy-2,4,6-trimethyl-benzyl chloride ($n_D^{27}=1.5415$) and reaction of the latter compound with triphenylphosphine. The 3-methoxy-2,4,6-trimethyl-benzyl-triphenylphosphonium chloride melts at 308°-310° C.

EXAMPLE 34

By the procedure described in Example 14, 9-(4-methoxy-3-allyl-2,6-dimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester is manufactured from 4-methoxy-3-allyl-2,6-dimethyl-benzyl-triphenylphosphonium chloride by reaction with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester. This product is converted by the procedure of Example 15 to 9-(4-methoxy-3-allyl-2,6-dimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid of melting point 160° C.-161° C.

The 4-methoxy-3-allyl-2,6-dimethyl-benzyl-triphenylphosphonium chloride employed as the starting material is prepared by the procedure described in Example 16 by haloformylation of 3,5-dimethyl-2-allyl-anisole to give 4-methoxy-3-allyl-2,6-dimethyl-benzyl chloride ($n_D^{20}=1.5690$) and reaction of the latter compound with triphenylphosphine.

EXAMPLE 35

By the procedure described in Example 14, 9-(4-methoxy-3-nitro-2,6-dimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester is manufactured from 4-methoxy-3-nitro-2,6-dimethyl-benzyl-triphenylphosphonium chloride by reaction with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid ethyl ester. This product is converted by the procedure of Example 15 to 9-(4-methoxy-3-nitro-2,6-dimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid of melting point 109°-110° C.

The 4-methoxy-3-nitro-2,6-dimethyl-benzyl-triphenylphosphonium chloride employed as the starting material is prepared by the procedure described in Example 16 by haloformylation of 2-nitro-3,5-dimethyl-anisole to give 4-methoxy-3-nitro-2,6-dimethyl-benzyl chloride (melting point 109°-110° C.) and reaction of the latter compound with triphenylphosphine. The 4-methoxy-3-nitro-2,6-dimethyl-benzyl-triphenylphosphonium chloride melts at 230°-232° C.

EXAMPLE 36

By the procedure described in Example 14, 9-(4-ethoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester (melting point 96°-97° C.) is manufactured from 4-ethoxy-2,3,6-trimethyl-benzyl-triphenylphosphonium chloride by reaction with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid ethyl ester.

The 4-ethoxy-2,3,6-trimethyl-benzyl-triphenylphosphonium chloride employed as the starting material is

prepared by the procedure described in Example 15 by alkylation of 2,3,5-trimethylphenol to give 2,3,5-trimethyl-phenyl ethyl ether (melting point 93°-95° C), by haloformylation of the ether obtained to give 4-ethoxy-2,3,6-trimethyl-benzyl chloride (melting point 63°-64° C.) and by reaction of the latter compound with triphenylphosphine

EXAMPLE 37

By the procedure described in Example 14, 9-(4-isopropoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester is manufactured from 4-isopropoxy-2,3,6-trimethyl-benzyl-triphenyl-phosphonium chloride by reaction with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid butyl ester. This product, is converted by the procedure of Example 15 to 9-(4-isopropoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid of melting point 176°-177° C.

The 4-isopropoxy-2,3,6-trimethyl-benzyl-triphenyl-phosphonium chloride employed as the starting material is prepared by the procedure described in Example 18 by alkylation of 2,3,5-trimethylphenol to give 2,3,5-trimethylphenyl isopropyl ether (boiling point 115° C./11 mmHg), by haloformylation of the ether obtained to give 4-isopropoxy-2,3,6-trimethyl-benzyl chloride ($n_D^{20} = 1.5433$) and by reaction of the latter compound with triphenylphoshine.

EXAMPLE 38

By the procedure described in Example 14, 9-(3-dimethylamino-2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester (bright-yellow oil) is manufactured from 3-dimethylamino-2,4,6-trimethyl-benzyltriphenylphosphonium chloride by reaction with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid ethyl ester.

The 3-dimethylamino-2,4,6-trimethyl-benzyl-triphenylphosphonium chloride employed as the starting material is prepared by the procedure described in Example 16 by haloformylation of N,N-dimethylmesidine to give 3-dimethylamino-2,4,6-trimethyl-benzyl chloride (boiling point 71° C./11 mmHg) and reaction of the latter compound with triphenylphosphine.

EXAMPLE 39

1.7 g of 8-diethoxy-phosphono-3,7-dimethyl-octa-2,4,6-trien-1-oic acid ethyl ester are introduced in 8.0 ml of tetrahydrofuran. The solution is cooled to 0° C. after addition of 0.27 g of sodiumhydride (50-60%), then stirred 30 minutes at 0° C. and thereafter a solution of 0.96 g of 2,3,6-trimethyl-p-anisaldehyde in 3 ml of tetrahydrofuran is added dropwise during 15 minutes. The reaction mixture is stirred 7 hours at room temperature, then poured into ice and, after addition of 2 N hydrochoric acid, extracted with diethyl ether. The ether extract is washed neutral with water, dried over sodium sulfate and evaporated under reduced pressure. The remaining 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester melts at 104°-105° C.

Instead of sodium hydride (0.27 g), employed above, an alkali metal alcoholate can also be used as condensation agent, e.g. sodium ethylate (0.125 g of sodium in 5 ml ethanol).

EXAMPLE 40

3.03 g of 8-bromo-3,7-dimethyl-octa-2,4,6-trien-1-oic acid ethyl ester are heated with 1.66 g of triethylphosphite slowly to 125° C. The surplus bromo ester is distilled off. The residue is cooled and poured into ice and extracted with diethyl ether and an aqueous soution of sodium-hydrogen carbonate, dried and evaporated under reduced pressure. The remaining 8-diethoxyphosphono-3,7-dimethyl-octa-2,4,6-trien-1-oic acid ethyl ester is immediately treated, as described above, with 2,3,6-trimethyl-p-anisaldehyde.

EXAMPLE 41

2 g of 1-(phenyl-sulfonyl)-methyl-4-methoxy-2,3,6-trimethyl-benzene are introduced in 10 ml of tetrahydrofuran. The solution is cooled to −78° C. and, after the addition of 0.51 g of butyl lithium, treated with a solution of 1.8 g 8-bromo-3,7-dimethyl-octa-2,4,6-trien-1-oic acid ethyl ester in 8 ml of tetrahydrofuran. The reaction mixture is stirred 2 hours at −78° C., 2 hours at −40° C. and 16 hours at 0° to +5° C. The mixture is poured into ice and, after addition of 2 N hydrochloric acid, extracted with diethyl ether. The ether extract is washed neutral with water, dried over sodium sulfate and evaporated under reduced pressure. The remaining 9-(4-methoxy-2,3,6-trimethyl-phenyl)-9-(phenyl-sulfonyl)-3,7-dimethyl-nona-2,4,6-trien-1-oic acid ethyl ester (2.8 g) is diluted with 8 ml of abs. ethanol. The solution is treated at 0° C. in 2 portions with 1.2 g of sodium ethylate powder. The mixture is stirred 30 minutes at 0° C., then 2 hours at 80° C., thereafter cooled, poured into ice and, after the addition of 2 N hydrochloric acid, extracted with diethyl ether. The ether extract is washed neutral with water, dried over sodium sulfate and evaporated under reduced pressure. The remaining 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester melts at 105° to 105° C.

EXAMPLE 42

16.8 g of 4-methoxy-2,3,6-trimethyl-benzyl alcohol, 17.4 g of sodium salt of benzene sulfinic acid, 20.0 ml of isopropanol and 30.0 ml of glacial acetic acid are heated 16 hours under nitrogen and reflux conditions. The reaction mixture is cooled, treated portionwise with 200 ml of water and neutralized by the addition of sodium hydrogen carbonate. The organic layer is separated, washed several times with an aqueous solution of sodium hydrogen-carbonate (5% by weight), dried over sodium sulfate and evaporated under reduced pressure. The remaining 1-(phenyl-sulfonyl)-methyl-4-methoxy-2,3,6-trimethyl-benzene shows the following I.R.: 1592, 1580, 1302, 1149, 118 cm^{-1}.

EXAMPLE 43

1.08 g of 4-methoxy-2,3,6-trimethyl-benzylchloride, 1.67 g of 8-(phenyl-sulfonyl)-3,7-dimethyl-octa-2,4,6-trien-1-oic acid ethyl ester and 10 ml of dimethylformamide are cooled to 0° C. and treated with 0.374 of solid sodium ethanolate. The reaction mixture is stirred 30 minutes at room temperature, then poured into ice and, after the addition of 2N hydrochloric acid, extracted with diethyl ether. The ether extracted is washed neutral, dried over sodium sulfate and evaporated under reduced pressure. The remaining 9-(4-methoxy-2,3,6-trimethyl-phenyl)-8-(phenyl-sulfonyl)-3,7-dimethyl-nona-2,4,6,8-trien-1-oic acid ethyl ester is (as described

in Example 42) with the formation of benzene sulfonic acid as side product and additional carbon-carbon double bond in the main product, transformed into the desired 9-(4-methoxy-2,3,6-trimethyl-phenyl9-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester (m.p. 104°-105° C.).

EXAMPLE 44

8.5 g of 8-bromo-3,7-dimethyl-octa-2,4,6-trien-1-oic acid ethyl ester are dissolved into 95 ml of dimethyl sulfoxide The solution is treated under nitrogen in the cold with 0.45 g of sodium salt of benzene sulfinic acid. The mixture is stirred 1 hour at room temperature, then poured into ice and extracted with diethyl ether. The ether extract is washed with water dried over sodium sulfate and evaporated under reduced pressure. The remaining 8-(phenyl-sulfonyl)-3,7-dimethyl-octa-2,4,6-trien-1-oic acid ethyl ester melts at 114°-115° C.

EXAMPLE 45

By the procedure of Example 21:

9-(4-methoxy-2,3,5,6-tetramethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester (melting point 105°-106° C.) is manufactured from 9-(4-methoxy-2,3,5,6-tetramethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid and ethyl iodide;

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid 2-diethylaminoethyl ester (bright-yellow oil) is manufactured from 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid and diethylaminoethyl chloride;

and 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid (3-pyridyl) methyl ester (melting point 113°-114° C.) is manufactured from 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid and beta-picoline chloride.

EXAMPLE 46

20 g of 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid dissolved in 200 ml of tetrahydrofuran. After the addition of 5.5 ml of phosphorus trichloride, the solution is stirred for 2 hours at room temperature, cooled to 0° C. and treated firstly with 50 ml of pyridine and then dropwise at 0°-5° C. with 50 ml of propargyl alcohol. The mixture is stirred for 2 hours at room temperature and then diluted with water. The organic phase is washed successively with water, dilute hydrochloric acid and a 2% aqueous sodium bicarbonate solution, dried over sodium sulphate and evaporated. There is obtained 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethylnona-2,4,6,8-tetraen-1-oic acid propargyl ester which melts at 94°-95° C. after absorption on aluminium oxide using benzene as the eluent.

EXAMPLE 47

By the procedure of Example 46:

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid allyl ester (melting point 66°-68° C.) is manufactured from 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid and allyl alcohol.

EXAMPLE 48

By the procedure of Example 23:

9-(4-methoxy-2,3,5,6-tetramethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethylamide (melting point 200°–201° C.) is manufactured from 9-(4-methoxy-2,3,5,6-tetramethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid chloride and ethylamine,

and 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid morpholide is manufactured from 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid chloride and morpholine.

EXAMPLE 49

15 g of 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester (50:50 cis/trans mixture) are chromatographed on 1.5 kg of aluminum oxide (activity stage 1) using hexane/-diethyl ether (80:20 parts by volume) as the eluent. From the front, there is isolated 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2-trans,4-cis,6-trans,8-trans-tetraen-1-oic acid ethyl ester as a light-yellow oil.

EXAMPLE 50

The 4-methoxy-2,3,5-trimethyl-benzyl-triphenyl-phosphonium chloride employed as the starting material in Example 51 is prepared in a manner analogous to that described in the aforegoing Example 8, e.g., by the following sequence:

2,3,6-trimethylphenol
2,3,6-trimethylanisole
4-methoxy-2,3,5-trimethyl-benzyl chloride.

EXAMPLE 51

In analogy to the procedure given in Example 6: 4-methoxy-2,6-dimethyl-3-ethyl-benzyl-triphenyl-phosphonium chloride is condensed with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid ethyl ester to produce 9-(4-methoxy-2,6-dimethyl-3-ethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester which is converted by the procedure of Example 7 to form 9-(4-methoxy-2,6-dimethyl-3-ethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid, m.p.: 197°–198° C.

EXAMPLE 52

The 4-methoxy-2,6-dimethyl-3-ethyl-benzyl-triphenylphosphonium chloride employed as the starting material in Example 53 can be prepared in a manner analogous to that described in Example 8 by the following sequence:

3,5-dimethylphenol
1-acetoxy-3,5-dimethyl-benzene
2-acetyl-3,5-dimethyl-phenol
2-ethyl-3,5-dimethyl-phenol
2-ethyl-3,5-dimethyl-anisole
4-methoxy-2,6-dimethyl-3-ethyl-benzyl chloride.

EXAMPLE 53

In analogy to the procedure given in Example 6: 4-methoxy-3,5-diethyl-2,6-dimethyl-benzyl-triphenylphosphonium chloride is condensed with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid ethyl ester to produce the 9-(4-methoxy-3,5-diethyl-2,6-dimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester which is converted by the procedure of Example 7 to 9-(4-methoxy-3,5-diethyl-2,6-dimethyl-phenyl)-acid, m.p. 153°–154° C.

EXAMPLE 54

The 4-methoxy-3,5-diethyl-2,6-dimethyl-benzyl-triphenylphosphonium chloride employed as starting materials in Example 55 can be prepared in a manner analogous to that described in Example 8 by the following sequence:

3,5- dimethyl-phenol
1-acetoxy-3,5-dimethyl-benzene
2-acetyl-3,5-dimethyl-phenol
2-ethyl-3,5-dimethyl-phenol
1-acetoxy-2-ethyl-3,5-dimethyl-benzene
6-acetyl-2-ethyl-3,5-dimethyl-phenol
2,6-diethyl-3,5-dimethyl-phenol
2,6-diethyl-3,5-dimethyl-anisole
4-methoxy-3,5-diethyl-2,6-dimethyl-benzyl chloride.

EXAMPLE 55

In analogy to the procedure given in Example 6:

4-propoxy-2,3,6-trimethyl-benzyl-triphenyl-phosphonium chloride is condensed with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid ethyl ester to produce 9-(4-propoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester which is converted by the procedure of Example 7 to 9-(4-propoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1 oic acid, m.p.: 200°–201° C.

EXAMPLE 56

The 4-propoxy-2,3,6-trimethyl-benzyl-triphenylphosphonium chloride employed as starting material, can be prepared in a manner analogous to that described in Example 8, e.g., by the following sequence:

2,3,5-trimethylphenol
2,3,5-trimethyl-propoxy-benzene
4-propoxy-2,3,6-trimethyl-benzyl chloride.

EXAMPLE 57

In analogy to the procedure given in Example 6:

4-ethoxy-2,3,6-trimethyl-benzyl-triphenyl-phosphonium chloride is condensed with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid ethyl ester to produce 9-(4-ethoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetranoic acid ethyl ester which is converted by the procedure of Example 7 to 9-(4-ethoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid, m.p. 219°–220° C.

EXAMPLE 58

By the procedure of Example 6:

3,5-dichloro-2,4,6-trimethyl-benzyl-triphenyl-phosphonium chloride is condensed with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid ethyl ester to form 9-(3,5-dichloro-2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester which is converted by the procedure of Example 7 to 9-(3,5-dichloro-2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid, m.p: 220°–222° C.

EXAMPLE 59

In analogy to the procedure given in Example 6:

3-chloro-2,4,6-trimethyl-benzyl-triphenyl-phosphonium chloride is condensed with 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid ethyl ester to produce 9-(3-chloro-2,4,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-oic acid ethyl ester, m.p.: 84°–85° C.

EXAMPLE 60

The 3-chloro-2,4,6-trimethyl-benzyl-triphenylphosphonium chloride employed as starting material, can be prepared in a manner analogous to that described in the aforegoing Example 8, e.g., by the following sequence:
2,4,6-trimethyl-aniline
2,4,6-trimethyl-chlorobenzene
3-chloro-2,4,6-trimethyl-benzyl chloride.

EXAMPLE 61

36.5 g. of 1-ethoxycarbonyl-2,6-dimethyl-hepta-1,3,5-trien-7-triphenylphosphonium bromide are dissolved in 200 ml. of dimethylformamide. The solution is, after addition of 15.0 g. of 4-methoxy-3-butyl-2,6-dimethyl benzlaldehyde, treated at 10° C. dropwise with a solution of 1.64 g. of sodium in 40 ml. of absolute ethanol. The mixture is subsequently stirred for 12 hours at room temperature, then introduced into 500 ml. of methanol/-water 60:40 parts by volume and thoroughly extracted with hexane. The hexane extract is washed with methanol/water 60:40 parts by volume, then with water, dried over sodium sulfate and evaporated. There is obtained 9-(4-methoxy-3-butyl-2,6-dimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester, which is converted, as described in Example 7, into 9-(4-methoxy-3-butyl-2,6-dimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid; m.p.: 147°–148° C.

EXAMPLE 62

294 ml. of butyric acid anhydride are treated, after the addition of 2 ml. of concentrated aqueous sulfuric acid, at room temperature with 122 g. of 3,5-dimethylphenol. The temperature rises to 40° C. and is then raised to 80° C. The mixture is stirred for 1 hour and diluted with 60 ml. of water and 60 ml. of ethanol, poured onto ice water and twice extracted with 500 ml. of hexane each time. The hexane extract is washed with water, aqueous sodium bicarbonate solution, dried over sodium sulfate and evaporated. There is obtained 1 butyryloxy-3,5-dimethyl-benzene which boils at 123°–125° C./11 mm Hg after rectification.

180 g. of 1-butyryloxy-3,5-dimethyl-benzene are treated at room temperature with 340 g. of aluminium chloride. The mixture is stirred for 4 hours at 90°–95° C., then cooled at 70° C., poured onto ice and 3 n aqueous hydrochloric acid and extracted with ether. The ether extract is washed with water to neutral reaction, dried over sodium sulfate and evaporated. There is obtained 2-butyryl-3,5-dimethyl-phenol, which melts at 48°–52° C. after recrystallization from petroleum ether.

10 g. of 2-butyryl-3,5-dimethyl-phenol are dissolved in 100 ml. of glacial acetic acid. After the addition of 3 drops of perchloric acid, the solution is hydrogenated under normal conditions in the presence of 0.5 g. of platinum oxide. After the uptake of 3.0 l. of hydrogen, the hydrogenation is stopped. The catalyst is filtered off. The filtrate is extracted with ether. The ether extract is washed with water to neutral reaction, dried over sodium sulfate and evaporated. There is obtained 2-butyl-3,5-dimethylphenol, which melts at 65°–67° C. after absorption on silica gel, using methylene chloride/hexane 1:1 parts by volume as the eluent.

83 g. of 2-butyl-3,5-dimethyl-phenol are dissolved in 225 ml. of methanol. After the addition of 60 g. of potassium hydroxide in 25 ml. of water, the solution is treated at room temperature with 34.2 g. of methyl iodide. The mixture is heated to boiling under reflux conditions for

3 hours, then cooled, diluted with water and extracted with ether. The ether extract is washed with diluted sodium hydroxide solution, dried over sodium sulfate and evaporated. There is obtained 2-butyl-3,5-dimethyl-anisole, which is purified by absorption on silica gel, using hexane/methylene chloride 70:30 parts by volume as the eluent, before processing further

5.5 ml. of phosphorous oxychloride are added dropwise while stirring to 4.6 ml. of dimethylformamide. The temperature rises to 30° C. The mixture is treated dropwise with 9.6 g. of 2-butyl-3,5-dimethylanisole, poured onto ice water after the addition of 30 to 35 percent aqueous solution of sodium acetate, stirred for 1 hour and extracted with benzene. The benzene extract is washed with water, dried over sodium sulfate and evaporated. There is obtained 4-methoxy-3-butyl-2,6-dimethyl-benzaldehyde, which is purified by absorption on silica gel, using hexane/methylene chloride 1:1 parts by volume as the eluent, before the condensation with 1-ethoxycarbonyl-2,6-dimethyl-hepta-1,3,5-trien-7-triphenylphosphonium bromide.

EXAMPLE 63

36 g. of 7-formyl-3-methyl-octa-2,4,6-trien-1-oic acid ethyl ester are dissolved in 600 ml. of absolute ethanol. The solution is treated portionwise with 1.8 g. of sodium borohydride. The mixture is stirred for 2 hours at 10° C., then poured onto ice water and 3 n aqueous hydrochloric acid and extracted with ether. The ether extract is washed successively with water, a saturated aqueous sodium bicarbonate solution and once more with water, dried over sodium sulfate and evaporated. There is obtained 8-hydroxy-3,7-dimethyl-octa-2,4,6-trien-1-oic acid ethyl ester, which is processed further as follows:

36.5 g. of 8-hydroxy-3,7-dimethyl-octa-2,4,6-trien-1-oic acid ethyl ester are dissolved in 380 ml. of ether. The solution is cooled to 0° C., and after the addition of 3 drops of pyridine treated dropwise with 28.6 g. of phosphorous tribromide in 120 ml. of hexane. The mixture is stirred for 20 minutes at 0° C., then poured onto ice water and extracted with ether. The ether extract is washed successively with water, a saturated aqueous sodium bicarbonate solution and again with water, dried over sodium sulfate and evaporated. There is obtained 8-bromo-3,7-dimethyl-octa-2,4,6-trien-1-oic acid ethyl ester, which is processed as follows:

43.7 g. of 8-bromo-3,7-dimethyl-octa-2,4,6-trien-1-oic acid ethyl ester are dissolved in 500 ml. of benzene and treated with 42.0 g. of triphenylphosphine. The mixture is stirred for 12 hours at room temperature, then cooled at 0° C. The precipitated 1-ethoxycarbonyl-2,6-dimethyl-hepta-1,3,5-trien-7-triphenylphosphonium bromide melts at 193°-194° C.

EXAMPLE 64

In analogy to the procedure given in Example 61:

3,4-dimethoxy-2,6-dimethyl-benzaldehyde is condensed with 1-ethoxycarbonyl-2,6-dimethyl-hepta-1,3,5-trien-7-triphenylphosphonium bromide to produce 9-(3,4-dimethoxy-2,6-dimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester which is converted by the procedure of Example 7 to 9-(3,4-dimethoxy-2,6-dimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid, m.p.: 203°-204° C.

EXAMPLE 65

The 3,4-dimethoxy-2,6-dimethyl-benzaldehyde employed as starting material, can be prepared in a manner analogous to that described in Example 64 by the following sequence:

2,4-dimethylphenol
2,4-dimethyl-6-nitro-phenol
2,4-dimethyl-6-nitro-anisole
2,4-dimethyl-6-amino-anisole
2,4-dimethyl-6-hydroxy-anisole
2,4-dimethylveratrole.

EXAMPLE 66

In analogy to the procedure given in Example 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid chloride is reacted with methyl-amine to produce 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid methyl amide, m.p. 206° C.;

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid chloride is reacted with isopropyl amine to produce 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid isopropyl amide, m.p. 200° C.;

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid chloride is reacted with butyl amide to produce 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl amide, m.p. 178° C.; and

9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid chloride is reacted with hexylamide to produce 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid hexylamide, m.p. 157°–158° C.

EXAMPLE 67

9-(4-Methoxy-2,3,6-Trimethylphenyl)-3,7-Dimethyl-2,4,6,8-Nonatetraen-1-ol

In a 5-liter, round bottom flask provided with a stirrer, low temperature thermometer, an inlet for dry nitrogen, a gas outlet, and a dropping funnel connected to a mineral oil bubbler, were placed 150 g (0.436 moles) of 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid ethyl ester and 800 ml of toluene. The contents were stirred until the solids had dissolved, then by means of a dry ice bath, the internal temperature was lowered to −60° C., at which temperature 780 ml of a 25% solution of diisobutylaluminum (DIBAL) hydride in toluene (1.155 moles) was added dropwise. The initially yellow solution or suspension gradually deepened in color and after all the DIBAL had been added, the reaction mixture consisted of a clear, somewhat viscous deep red orange solution. After stirring for one hour, the cooling bath was lowered and the internal temperature allowed to rise to −40° C., at which temperature, 50 ml of a 50% aqueous methanol solution was added dropwise with intermittent cooling so that when the addition was complete the temperature was approximately 10° C. At this point, 140 ml of a saturated solution of sodium sulfate was added dropwise. Allowing the temperature to gradually rise to 25° C. Toward the end of the addition, aluminum hydroxide began to precipitate with the evolution of heat. After stirring for a few minutes, 800 ml of chloroform was added and the suspension stirred for ten minutes. The precipitate was removed by filtration on a twelve-

inch Buchner funnel through a layer of filter aid, then washed four times with 500 ml portions of chloroform. The combined filtrates were washed successively with 600 ml of water, 600 ml of water containing 10 ml of 3 N hydrochloric acid, 600 ml of saturated sodium bicarbonate solution, and 600 ml of water, then dried over anhydrous sodium sulfate. Distillation of the solvent in the rotary evaporator left 130-145 g of a crystalline residue. To this was added one liter of hexane and the suspension stirred vigorously until the aggregates had been dispersed, any material adhering to the walls was scraped off. The yellow crystalline precipitate was recovered by filtration, washed twice with sufficient hexane to cover the filter cake, then dried in vacuo first at 12-15 mm (water pump), then at 0.5 mm until the weight was constant. The yield of product was 119-123 g, m.p. 127.5°-129.5° C.

Distillation of the hexane from the filtrate and washings in the rotary evaporator left a residue of 12-15 g that crystallized very slowly, and yielded approximately 6-8 g of high quality material.

EXAMPLE 68

Methyl Ether of 9-(4-Methoxy-2,3,6-Trimethylphenyl)-3,7-Dimethyl-2,4,6,8-nonatetraene-1-ol

In a 5-l, round bottom flask flushed with nitrogen provided with a stirrer, thermometer, gas inlet tube, reflux condenser topped by a gas outlet connected to a mineral oil bubbler, and a six-inch length of Gooch tubing were placed 156 g (0.5 moles) of 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraene-1-ol, 564 g (4 moles) of methyl iodide and 2.5 l of tetrahydrofuran. To the stirred solution, at 20°-25° C., 24 g (1.0 moles) of sodium hydride were gradually added over a period of about one hour from a 500 ml Erlenmeyer flask connected through the Gooch tubing. The yellow solution became turbid and assumed a brownish tint. Within a few minutes the temperature rose to 28° C. but was maintained at 25° C. by external cooling. After 2.5 hours, the reaction vessel was cooled to 10° C. by an ice bath and the excess sodium hydride decomposed by the dropwise addition of 50% aqueous methanol. The solvent was then distilled in the rotary evaporator leaving a partially crystalline residue that was dissolved in 500 ml of benzene and transferred to a separatory funnel where it was washed successively with three 500-ml portions of saturated sodium bicarbonate solution and once with water containing a little sodium sulfate. To the benzene solution, 100 mg of butylated hydroxy toluene (BHT) was added, together with anhydrous sodium sulfate, then the solvent distilled in a rotary evaporator leaving 172 g of an orange syrup.

This syrup together with another 167 g of a similarly prepared lot was dissolved in 750 ml of warm hexane and filtered. The stirred solution was allowed to crystallize at room temperature for approximately one hour, then the crystallization completed at 0° C., all under nitrogen. The yellow orange crystalline product was recovered by filtration (nitrogen) and washed twice with hexane. After drying, first at 10-15 mm, and then at 0.5 mm to constant weight, 266 g (81%) of product was obtained m.p. 67.5°-69.5° C.

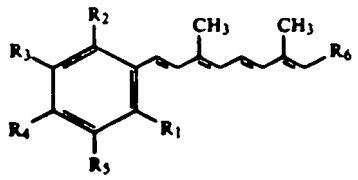
EXAMPLE 69

The n-Butyl Ether of 9-(4-Methoxy-2,3,6-Trimethylphenyl)-3,7-Dimethyl-2,4,6,8-Nonatetraen-1-ol

Under nitrogen, 6.0 g of 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nonatetraen-1-ol, (0.0192 moles) was dissolved in 150 ml of tetrahydrofuran containing 28.05 g of n-butyliodide in a 250 ml. round bottom, flask provided with a stirrer, thermometer, nitrogen inlet tube, and an opening for the addition of a solid, through which was added 0.92 g of sodium hydride. The mixture was stirred for 48 hours, then cooled, and the excess hydride decomposed by the cautious addition of methanol. The mixture was then diluted with 500 ml of water and extracted with three 50-ml portions of ether. After drying over magnesium sulfate, the solvent was distilled in the rotary evaporator and the residue taken up in ten ml of hexane. On addition of ten ml of methanol, 2.5 g of crystals of the starting material, m.p. 107°-112° C. were obtained. The filtrate, after removal of the solid, was freed of solvent and the residue was chromatographed on 200 g of silica gel. From the fraction eluted with 50% ether in hexane was obtained 2.6 g of a solid, which after recrystallization from methanol afforded 1.5 g of deep yellow crystals, m.p. 52°-54° C.

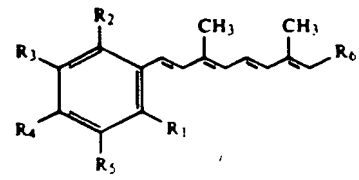
We claim:

1. A compound of the formula:



wherein R_1 and R_2 are lower alkyl; R_3 is hydrogen, lower alkyl, lower alkoxy, lower alkenyloxy, nitro, amino, lower alkylamino, lower alkanoylamino or N-heterocyclyl; R_4 is lower alkoxy; R_5 is hydrogen, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, nitro, amino, lower alkanoylamino, lower alkylamino or N-heterocyclyl; and R_6 is alkanoyloxymethylene, alkenyloxycarbonyl, alkynyloxycarbonyl, carbamoyl, mono(lower alkyl)-carbamoyl, di(lower alkyl)-carbamoyl, N-heterocyclylcarbonyl, or alkoxycarbonyl where its alkoxy moiety is unsubstituted or substituted with alkylamino, morpholino, piperdyl, pyridyl, alkyl substituted piperidyl or alkyl substituted pyridyl,
or pharmaceutically acceptable salts thereof.

2. A compound of the formula:



wherein R_1 and R_2 are lower alkyl; R_3 is hydrogen or lower alkyl; R_4 is lower alkoxy; R_5 is hydrogen, lower alkyl or lower alkoxy; and R_6 is alkoxycarbonyl or carbamoyl,
or pharmaceutically acceptable salts thereof.

3. The compound of claim 1 wherein R_6 is alkoxycarbonyl.

4. The compound of claim 3 wherein said compound is 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid methyl ester.

5. The compound of claim 3 wherein said compound is 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester.

6. The compound of claim 3 wherein said compound is 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2-trans,4-cis,6-trans,8-trans-tetraen-1-oic acid ethyl ester.

7. The compound of claim 3 wherein said compound is 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic isopropyl ester.

8. The compound of claim 3 wherein said compound is 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid butyl ester.

9. The compound of claim 3 wherein the alkoxy group of the alkoxycarbonyl moiety is substituted with alkylamino, morpholino, piperidyl, pyridyl, alkyl substituted piperidyl or alkyl substituted pyridyl.

10. The compound of claim 9 wherein said compound is 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid diethyl aminoethyl ester.

11. The compound of claim 9 wherein said compound is 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid (3-pyridyl)methyl ester.

12. The compound of claim 1 wherein R_6 is alkynyloxycarbonyl.

13. The compound of claim 12 wherein said compound is 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid allyl ester.

14. The compound of claim 1 wherein R_6 is alkynyloxycarbonyl.

15. The compound of claim 14 wherein said compound is 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-

dimethyl-nona-2,4,6,8-tetraen-1-oic acid propargyl ester.

16. The compound of claim 1 wherein R_6 is alkanoyloxymethylene.

17. The compound of claim 16 wherein said compound is 1-acetoxy-9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraene.

18. The compound of claim 1 wherein R_6 is carbamoyl

19. The compound of claim 18 wherein said compound is 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid amide.

20. The compound of claim 1 wherein R_6 is mono or dilower alkylcarbamoyl.

21. The compound of claim 20 wherein said compound is 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl amide.

22. The compound of claim 21 wherein said compound is 9-(4-methoxy-2,3,5,6-tetramethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl amide.

23. The compound of claim 20 wherein said compound is 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid diethylamide.

24. The compound of claim 1 wherein R_6 is N-heterocyclylcarbonyl.

25. The compound of claim 24 wherein said compound is 9-(4-methoxy-2,3,6-trimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid morpholide.

26. The compound of claim 1 wherein R_5 is lower alkenyl.

27. The compound of claim 1 wherein at least one of R_3 and R_5 is nitro and R_6 is alkoxycarbonyl.

28. The compound of claim 27 wherein said compound is 9-(4-methoxy-3-nitro-2,6-dimethyl-phenyl)-3,7-dimethyl-nona-2,4,6,8-tetraen-1-oic acid ethyl ester.

29. The compound of claim 1 wherein at least one of R_3 and R_5 is lower alkylamino and R_6 is alkoxycarbonyl.

30. The compound of claim 1 wherein at least one R_3 or R_5 is lower alkenyloxy.

EXHIBIT 3

HOFFMANN-LA ROCHE INC.

NUTLEY • NEW JERSEY • 07110

September 10, 1976

Division of Anti-Infective Drug Products
Bureau of Drugs HFD #140
Attention: DOCUMENT CONTROL ROOM #12B-30
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

Re: Form 1571 for Ro 10-9359

The sponsor, Hoffmann-La Roche Inc., is herewith submitting in triplicate Form FD 1571, a Notice of Claimed Investigational Exemption for a New Drug, for Ro 10-9359.

Schedules 1-5 and 7-10 are contained in Volume 1.1 of this submission. Schedule 6 is contained in Volumes 1.2, 1.3 and 1.4 of this submission. Tables of Contents for all Volumes follow immediately after Form FD 1571 in Volume 1.1; and, in addition, Volumes 1.2, 1.3 and 1.4 have their own Table of Contents.

We understand that no information contained in this Notice of Claimed Investigational Exemption for a New Drug, or in subsequent amendments thereto, will be made publicly available until an NDA for Ro 10-9359 is approved.

Additionally, in this Notice of Claimed Investigational Exemption for a New Drug, each page in Schedules 1-5, which pages contain the chemical structure, list of components, statement of composition, and methods of preparation and control, are marked "CONFIDENTIAL," as is each page in the Investigational Drug Brochure in Schedule 7 and the Plan of Investigation in Schedule 10, because the materials on these pages constitute trade secrets or information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552).

If for any reason Food and Drug Administration officials should at any time feel that disclosure of any of the materials marked "CONFIDENTIAL" should be made to any members of the public, we expect that because of the importance of maintaining confidentiality of these materials to Hoffmann-La Roche Inc. you will first consult with us on the issue of disclosure.

Sincerely,

HOFFMANN-LA ROCHE INC.

Allan S. Yard

Allan S. Yard, Ph.D.
Assistant Director
Drug Regulatory Affairs

ASY:gm
Enclosure
HLR No. 76991

EXHIBIT 4

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

RECEIVED
SEP 24 1976
DRA - Medical

IND 12,797

Hoffmann-La Roche, Incorporated
Attention: Allan S. Yard, Ph.D.
Nutley, New Jersey 07110

SEP 21 1976

Dear Dr. Yard:

We acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug as follows:

Sponsor: Hoffmann-La Roche, Incorporated

Name of Drug: Ro 10-9359 Capsules and Solution Oral

Date of Notice: September 10, 1976

Date of Receipt: September 14, 1976

IND Number Assigned: 12,797

Assignment of this number is for record keeping purposes only. All submissions must be made in triplicate and identified with this number.

We will communication with you further, should it be necessary, following our complete review of the preclinical data, manufacturing controls, and clinical protocol.

Progress reports are required at intervals not exceeding one year. Notify us promptly of discontinued studies and the reasons therefore. Where applicable, inform investigators of the discontinuance and take appropriate action with respect to unused supplies of the drug.

In the meantime you are responsible for compliance with the applicable provisions of the Food and Drug Act and the Regulations. This includes the immediate reporting of any alarming reactions.

Sincerely yours,

Donald A. Fowler

Donald A. Fowler
Supervisory Consumer Safety Officer
Division of Anti-Infective
Drug Products
Bureau of Drugs

EXHIBIT 5

HOFFMANN-LA ROCHE INC.

NUTLEY • NEW JERSEY • 07110

December 20, 1984

Division of Anti-Infective Drug Products
Center for Drugs and Biologics, HFN-815
Attention: DOCUMENT CONTROL ROOM 12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: TEGISON® (etretinate) CAPSULES
NDA 19-369
Original New Drug Application

Submitted herewith is an original New Drug Application for etretinate, a retinoid, for oral use for severe recalcitrant psoriasis.

Contained herein are the technical, clinical and preclinical data of the New Drug Application. A completed Form FD 356H follows immediately after this transmittal letter. Included in this volume (1.1) is an introduction to the organization of the New Drug Application and an Overall Index of Data by Topic which provides an overview of the documents submitted to the New Drug Application according to the type of information submitted and the review responsibility at the Agency. Also included in this volume (1.1) is a Table of Contents organized according to Form FD 356H. A detailed Table of Contents of all volumes of the New Drug Application is located in Volume 1.2. An index to all clinical data is detailed in Item 11 (Volme 1.1).

We would like to request, at this time, a 1-A classification for etretinate. This drug is indicated for the treatment of severe recalcitrant psoriasis, especially of the erythrodermic or generalized pustular types, and is reserved for patients who are unresponsive to or intolerant of standard therapies. Severe recalcitrant psoriasis of the erythrodermic or generalized pustular types may be life-threatening and are indications of great medical need for which few effective therapies exist.

As agreed upon at the pre-NDA submission meeting held on August 2, 1984, case reports reflecting new data included in the efficacy and safety updates will be submitted as soon as they are available. The cutoff date for the original data base for this New Drug Application was February 1, 1983 for all protocols except Protocol 2404. The cutoff date for said protocol was August 1, 1983. The cutoff date for the updated data base for this New Drug Application was April 16, 1984. Also, as agreed, the efficacy and safety updated data (Volumes 1.21, 1.24 through 1.42) have been pooled rather than updating each individual or pooled study report. However, we have included an updated study report for the one study (Protocol 2404A) in which new patients were entered during the update interval (Volume 1.22). Also included is a clinical study report for Protocol 2548 (Volume 1.21) which was not incorporated in the original clinical data base. The updated overall efficacy and safety evaluations (Volumes 1.21 and 1.24) include all data included in the original data base, all subsequent data for patients continuing on chronic therapy during the update interval and data for new patients studied under Protocols 2404A and 2548.

The NDA number, 19-369, was preassigned to the etretinate New Drug Application on October 1, 1984, as confirmed by Mr. Paul Chapman, Drug Application Document Control Center.

We are also submitting desk review copies of relevant sections of the NDA as discussed with Mr. David Bostwick on December 6, 1984. These are as follows:

1) DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Medical Reviewing Officer

Volume 1.1	(Organization of NDA, Overall Index of Data by Topic, Table of Contents according to Form FD 356H, Items 2.a., 12.g., 2.b., Highlights of Preclinical and Clinical Studies, Overall Summary of Clinical Data, Package Inserts, Location of Documents for Clinical Data)

Consumer Safety Officer

Volume 1.1	(Organization of NDA, Overall Index of Data by Topic, Table of Contents according to Form FD 356H, Items 2.a., 12.g., 2.b., Highlights of Preclinical and Clinical Studies, Overall Summary of Clinical Data, Package Inserts, Location of Documents for Clinical Data)
Volume 1.2	(Tables of Contents for all volumes)

2) DIVISION OF BIOMETRICS

Volume 1.1	(Overall Index of Data by Topic, Table of Contents according to Form FD 356H, Items 2.a., 12.g., 2.b., Highlights of Preclinical and Clinical Studies, Overall Summary of Clinical Data, Package Inserts, Location of Documents for Clinical Data)
Volume 1.4	(Introduction and Explanation of Criteria of Evaluation)
Volume 1.5	(Overall Efficacy Evaluation)
Volumes 1.6-1.20	(Overall Safety Evaluation)
Volume 1.21 (pages 1-14)	(Updated Overall Efficacy Evaluation)
Volumes 1.24-1.42	(Updated Safety Evaluation)
	Pooled/Individual Study Reports (includes statistical reports):

Volumes 1.49-1.56	(Pivotal Studies)
Volumes 1.57-1.75	(Supportive Studies)
Volume 1.21 (pages 42-73)	(Study Report Protocol 2548)
Volume 1.22	(Updated Study Report for Protocol 2404A)
Volume 1.23	(Case Report Summaries for 2404A update)
Volume 1.76	(Other Diagnoses)
Volume 1.77	(Protocols)
Volume 1.21 (pages 15-41)	(Amended Protocols for 2548 and 2404A)

3) DIVISION OF BIOPHARMACEUTICS

Volume 1.1	(Organization of NDA, Overall Index of Data by Topic, 2.a., 12.g., Highlights of Preclinical and Clinical Pharmacokinetics, Package Inserts, Item 11)
Volumes 1.45-1.48	(Pharmacokinetics/Biopharmaceutics Overall Summary and Reports)
Volume 1.77 (pages 1-106)	(Protocols for Pharmacokinetic Studies)
Relevant sections of of volumes 1.117, 1.118	(Technical Data)

The desk review copies are being sent to the attention of Mr. David Bostwick of the Division of Anti-Infective Drug Products for distribution within the Agency.

We understand that this New Drug Application and all information contained herein, unless otherwise made public by Hoffmann-La Roche Inc., is confidential and will remain so subsequent to approval of the NDA for this drug. If for any reason Food and Drug Administration officials should at any time feel that disclosure of any of the materials contained in this NDA should be made to any member of the public, we expect that because of the importance of maintaining confidentiality of these materials to Hoffmann-La Roche Inc., you will first consult with us on the issue of disclosure.

Please refer any inquiries or questions on this New Drug Application to the undersigned (telephone: 201-235-5402) or to Ms. June Anderson (telephone: 201-235-4693).

Sincerely,

HOFFMANN-LA ROCHE INC.

Karen K Church

Karen K. Church
Associate Director
Drug Regulatory Affairs

KKC/cw
HLR No. 84928

Enclosures: Form FDA 356H
346 Volumes (ribbon copy)
158 Volumes (copy No. 2)
139 Volumes (copy No. 3)
80 Volumes (desk review copies)
723 Volumes Total

EXHIBIT 6

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 24 1984

NDA 19-369

Karen K. Church
Hoffmann-LaRoche, Inc.
3401 Kingsland Street
Nutley, NJ 07110

Dear Dr. Church:

We are please to acknowledge your New Drug Application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug: Tegison (etretinate) Capsules

Date of Application: December 20, 1984

Date of Receipt: December 19, 1984

Our Reference Number: NDA 19-369

We will correspond with you further after we have had the opportunity to study the application. Should you have any questions prior to our contacting you, please call:

Mr. David Bostwick
301-443-4280

Sincerely yours,

Donald A. Fowler
Supervisory Consumer Safety Officer
Division of Anti-Infective
Drug Products
Office of Biologics Research and Review
Center for Drugs and Biologics

Received
Drug Regulatory Affairs

EXHIBIT 7

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 30 1986

NDA 19-369

Linda S. Dujack, Ph.D.
Hoffmann-La Roche, Inc.
Nutley, New Jersey 07110

Dear Dr. Dujack:

Reference is made to your New Drug Application dated December 20, 1984, submitted pursuant to section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Tegison (etretinate) Capsules.

Reference is also made to your additional communications dated August 5, September 10 and September 25, 1986.

We have completed the review of this application as amended and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on September 25, 1986. Accordingly, the application is approved, effective on the date of this letter.

Please submit the following when available:

1. Twelve copies of the final printed Patient Information Folder.

2. One market package of each size of the drug.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

for Elaine C. Esber, M.D.
Director
Office of Biologics Research and Review
Center for Drugs and Biologics

RECEIVED IN
DRUG REGULATORY AFFAIRS
OCT 3 1986

EXHIBIT 8

A BRIEF DESCRIPTION OF THE ACTIVITIES UNDERTAKEN
DURING THE APPLICABLE REGULATORY REVIEW PERIOD
WITH RESPECT TO THE APPROVED PRODUCT
AND THE SIGNIFICANT DATES APPLICABLE TO SUCH ACTIVITIES

TESTING PHASE

IND 12,797

9/10/76	Letter to FDA	Submitted original Form FD 1571, Notice of Claimed Investigational Exemption for a New Drug ("IND") for Ro 10-9359.*
9/21/76	Letter from FDA	FDA acknowledged receipt of IND submitted September 10, 1976 and assigned IND #12,797.
12/7/76	Letter from FDA	FDA requested additional data regarding controls portion of application.

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* Also referred to as "etretinate" or "Tegison ® ".

1/7/77	Letter to FDA	Submitted addenda to Schedules 2-5, current manufacturing controls for Ro 10-9359 25 mg capsules and placebo capsules, as well as toxicity data obtained with these capsules.
1/17/77	Letter to FDA	Addendum to Schedule 10 - Protocol #898A.
1/20/77	Letter to FDA	Confirmed telephone conversation regarding pilot studies carried out by National Cancer Institute in rats.
1/28/77	Letter to FDA	Submitted additional information on controls for Ro 10-9359, preliminary reports of studies in rats, addendum to Schedule 7 revising

		Investigational Drug Brochure, and addendum to Schedule 9 adding investigators.
3/3/77	Letter from FDA	Recommended thorough teratological studies be performed in at least two animal species.
3/11/77	Letter to FDA	Progress report concerning rat studies.
4/27/77	Letter from FDA	Requested additional data to submission of January 7, 1977.
9/9/77	Letter to FDA	Annual progress report.
9/27/77	Letter to FDA	Reply to FDA letter of March 3, 1977 submitting several volumes of unpublished teratological studies.

12/20/77	Letter to FDA	Addendum to Schedule 9 added investigator.
12/23/77	Letter to FDA	Submitted manufacturing controls for Ro 10-9359, Mouse Toxicity Data, Addendum to Schedule 10 - Protocol #1037, Addendum to Schedule 9, and Addendum to Schedule 7.
1/30/78	Letter to FDA	Addendum to Schedule 9.
2/21/78	Letter to FDA	Addendum to Schedule 9.
3/6/78	HLR Memo	Record of telephone communication with Anti-Infective Division, FDA regarding a proposed meeting.
3/15/78	Letter to FDA	Confirming telephone conversation of March 8, 1978 with FDA.

6/8/78	Letter to FDA	Addendum to Schedule 10 - Amended Protocol #1037.
6/20/78	Letter to FDA	Addendum to Schedule 10 - Amended Protocol #898A.
7/7/78	Letter to FDA	Addendum to Schedule 4.
7/26/78	Letter to FDA	Advised FDA of investigator's request to continue treatment beyond the 4 month treatment period pursuant to Protocol #1073.
8/4/78	Letter to FDA	Addendum to Schedule 10 - Amended Protocol #1037.
8/15/78	HLR Memo	Recorded telephone communication with Anti-Infective Division regarding requested extension of therapy in a patient pursuant to Protocol #1037.

9/8/78	Letter to FDA	Submitted annual progress report - clinical and preclinical data.
9/28/78	Letter to FDA	Addendum to Schedule 10 - Amended Protocol #1037, submitted an internal research report of clinical studies performed abroad and submitted copy of an amendment to the Investigational Drug Brochure.
10/11/78	Letter to FDA	Addendum to Schedule 10 - Protocol #898A.
10/16/78	HLR Memo	Recorded telephone communication from FDA on October 13, regarding HLR's submission to FDA of September 27, 1977.

10/20/78	HLR Memo	Recorded telephone communication from Anti-Infective Division, FDA requesting information on Ro 10-9359.
10/24/78	Letter to FDA	Addendum to Schedule 5.
1/29/79	Letter from FDA	Advised that amendment to Protocol #1037 submitted September 28, 1978 has been termed "satisfactory".
3/6/79	Letter from FDA	Requesting additional protocols and clarification of codes used by HLR.
4/24/79	Letter to FDA	Addendum to Schedule 9 and 10.
5/14/79	Letter to FDA	Response to FDA letter 3/6/79, regarding preclinical studies on Ro 10-9359.
5/22/79	Letter to FDA	Addendum to Schedule 9.

6/21/79	Letter to FDA	Submitted data and protocols to FDA regarding Ro 10-9359.
7/17/79	Letter to FDA	Reported information on patient.
8/17/79	Letter to FDA	Reported information on patient.
9/10/79	Letter to FDA	Submitted Annual Progress Report.
1/22/80	Letter to FDA	Addendum to Schedule 10 - Amendment to Protocols 2057 and 1037.
3/11/80	Letter to FDA	Addendum to Schedule 5.
3/28/80	Letter to FDA	Reported information on patient.
5/1/80	Letter to FDA	Addendum to Schedule 10 - Amendment to Protocol #1037 and Protocol 2057.

5/15/80	Letter to FDA	Addendum to Schedules 9 and 10.
6/17/80	Letter to FDA	Reported clinical information on female patients in Europe. Also submitted addendum to Schedules 9 and 10.
7/11/80	Letter to FDA	Submitted Addendum to Schedule 9, Addendum to Schedule 10 - Protocol #2184 and information on patient.
8/4/80	Letter to FDA	Submitted additional information regarding HLR submission of 6/17/80 and additional data on a patient.
8/15/80	Letter to FDA	Reported information on a patient.

9/5/80	Letter to FDA	Submitted Annual Progress Report, as well as Addenda to Schedule 6.
9/10/80	Letter to FDA	Submitted Addendum to Schedule 9 and Addendum to Schedule 10 - Protocol #2184.
11/7/80	Letter to FDA	Submitted Addendum to Schedule 9, additional Protocol #2244A, and data on a patient.
11/19/80	Letter to FDA	Addendum to Schedule 9 and 10.
12/4/80	HLR Memo	Summerized telephone conversation with Anti-Infective Division, FDA concerning HLR Annual Progress Reports submitted 9/5/80.

1/28/81	Letter to FDA	Revised specifications and directions for testing submitted to Schedule 5. Additionally, data on a patient was reported.
4/22/81	Letter to FDA	Submitted addendum to Schedule 7 and additional information on a patient.
5/20/81	Letter to FDA	Amended Protocol Nos. 2184 and 2187.
6/10/81	Letter to FDA	Reported information on a patient further to HLR's 7/17/79 letter to FDA.
7/29/81	HLR Memo	Reported telephone call from Anti-Infective Division, FDA requesting information.
8/4/81	Letter to FDA	Response to FDA's questions of 7/29/81 regarding preclinical studies on rats.

8/5/81	Letter to FDA	Submitted revised specifications and directions for testing for Schedule 5. Addendum to Schedule 9.
9/10/81	Letter to FDA	Submitted Annual Progress Report.
11/3/81	Letter to FDA	Reported information on patients and added investigator and protocol.
12/4/81	Letter to FDA	Reported information on patients and addendum to Schedule 9.
1/14/82	Letter to FDA	Addendum to Schedule 9 and reported information on patients.
2/12/82	Letter to FDA	Submitted Addendums to Schedules 9 and 10, as well

		as Protocol #2409A and additional information on patients.
2/18/82	Letter to FDA	Addendum to Schedule 9.
3/17/82	Letter to FDA	Submitted information regarding Schedules 1-5.
3/26/82	Letter to FDA	Submitted information on patients and an Addendum to Schedule 9.
5/25/82	Letter to FDA	Submitted an Addendum to Schedule 9, additional information on patients and additional Protocol #2403.
6/30/82	Letter to FDA	Submitted an Addendum to Schedule 9, additional information on patients, Addendum to Schedule 10 - Amendment of Protocol #2366A, and new Protocol #2548.

7/28/82	Letter to FDA	Submitted Schedules 2 through 5.
7/30/82	Letter to FDA	Submitted information on patients and amendments to Protocol #1037.
9/10/82	Letter to FDA	Submitted Annual Progress Report.
10/20/82	Letter to FDA	Submitted Addendum to Schedule 9 and additional information on patients.
11/12/82	Letter to FDA	Submitted Addendum to Schedule 9 and additional information on patients.
1/24/83	Letter to FDA	Submitted preclinical report and additional information on patients.

3/14/83	Letter to FDA	Submitted Amendment to Protocol #2184 and Amendment to Protocol #2187 as well as additional information on patients.
4/7/83	Letter to FDA	Reported additional information on patients.
5/4/83	Letter to FDA	Reported information on patients.
7/5/83	Letter to FDA	Reported additional information on patients.
9/9/83	Letter to FDA	Submitted Annual Progress Report.
10/13/83	Letter to FDA	Submitted additional information on patients as well as Amendment to Protocol #2404 and Amendment to Protocol #1037A.

12/20/83	Letter to FDA	Addendum to Schedules 9 and 10 (Protocol 2698A).
2/24/84	Letter to FDA	Reported information on patient.
3/5/84	Letter to FDA	Reported additional information on patients.
3/6/84	Letter to FDA	Submitted new protocol #2815 and Addendums to Schedule 2-5.
3/20/84	Letter to FDA	Submitted Addendum to Schedule 9.
4/4/84	Letter to FDA	Submitted additional Protocol - N2467A, as well as Addendums to Schedule 2-5.
4/13/84	Letter to FDA	Reported information on patients.
4/19/84	Letter to FDA	Submitted information on patient.

5/2/84	Letter to FDA	Submitted Amendment to Protocol #2366A, as well as additional information on patients.
6/8/84	Letter to FDA	Requested meeting to discuss filing of a New Drug Application for Ro -10-9359.
6/11/84	Letter to FDA	Reported information on patient.
6/22/84	Letter to FDA	Reported information on patient.
6/27/84	Letter to FDA	Addendum to Schedule 9.
7/2/84	Letter to FDA	Reported Amendment to Protocol #2404A and Protocol #2184A, as well as additional information on patients.
7/13/84	Letter to FDA	Addendum to Schedule 9.

7/17/84	Letter to FDA	Addendum to Schedule 9.
7/18/84	Letter to FDA	Addendum to Schedule 9 and additional information on patients.
7/20/84	Letter to FDA	Addendum to Schedule 6.
8/6/84	Letter to FDA	Reported information on patients.
8/16/84	HLR Memo	Confirmed subjects discussed at meeting with FDA on 8/2/84, regarding forthcoming NDA request.
8/29/84	Letter to FDA	Responded to information requested by FDA on 8/2/84, regarding the effect of Ro 10-9359 on male reproduction.
9/19/84	Letter to FDA	Reported additional information on patients.
10/1/84	HLR Memo	Obtained NDA #19-369 from FDA for Ro 10-9359.

10/16/84	HLR Memo	Confirmed 10/24/84 telephone conversation requesting a pre-NDA meeting with the FDA chemist reviewer.
10/22/84	Letter to FDA	Submitted daft manufacturing controls for discussion at meeting to be held at FDA on 11/9/84.
11/15/84	HLR Memo	Summarized 11.9.84 pre-NDA technical meeting with FDA.
11/30/84	Letter to FDA	Submitted Annual Progress Report - five volumes.
12/5/84	Letter to FDA	Reported additional information on patients. Submitted Addendum to Schedule 9.
1/15/85	Letter to FDA	Reported additional information on patients and submitted Addendum to Schedule 9.

2/8/85	Letter to FDA	Reported additional information on patients and submitted Addendum to Schedule 9.
3/18/85	Letter to FDA	Reported information on patients.
3/22/85	Letter to FDA	Reported foreign adverse reaction data.
4/11/85	Letter to FDA	Reported patient information and added Protocol #N-2614A to Schedule 10. Submitted Addendum to Schedule 9 and submitted data on foreign adverse reactions.
5/1/85	Letter to FDA	Submitted information on domestic and foreign adverse experience and research report on acute oral toxicity testing in male mice.

5/30/85	Letter to FDA	Reported information on patients and submitted Addendum to Schedule 9.
7/10/85	Letter to FDA	Submitted information on patients and Addendum to Schedule 9.
7/25/85	Letter to FDA	Submitted information on patients.
9/13/85	Letter to FDA	Submitted information on patients and Addendum to Schedule 9.
9/30/85	Letter to FDA	Submitted Annual Progress Report - three volumes. Also submitted Addendum to Schedule 9.
10/4/85	Letter to FDA	Submitted information on patients and Addendum to Schedule 9.

10/31/85	Letter to FDA	Submitted information on patients and Addendum to Schedule 9.
11/11/85	Letter to FDA	Submitted information on patients.
12/18/85	Letter to FDA	Submitted information on patients and Addendum to Schedule 9.
1/17/86	Letter to FDA	Submitted information on patients and Addendum to Schedule 9.
2/3/86	Letter to FDA	Submitted information on patients and Addendum to Schedule 9.
2/11/86	Letter to FDA	Submitted information on patients and Addendum to Schedule 9.

2/24/86	Letter to FDA	Submitted information on patients and Addendum to Schedule 9.
2/27/86	Letter to FDA	Submitted information on patients.
3/12/86	Letter to FDA	Submitted information on patients.
3/27/86	Letter to FDA	Submitted information on patients.
3/28/86	Letter to FDA	Submitted information on patients and Addendum to Schedule 10.
4/1/86	Letter to FDA	Submitted information on patients and Addendum to Schedule 9.
4/2/86	Letter to FDA	Submitted information on patients.

4/11/86	Letter to FDA	Submitted information on patients and Addendum to Schedule 9.
4/18/86	Letter to FDA	Submitted information on patients.
5/2/86	Letter to FDA	Submitted information on patients and Addendum to Schedule 9.
5/7/86	Letter to FDA	Submitted information on patients.
5/16/86	Letter to FDA	Submitted information on patients and clinical investigators and addendum to schedule 9.
5/23/86	Letter to FDA	Submitted information on patient.
5/27/86	Letter to FDA	Submitted Addendum to Schedule 5.

6/9/86	Letter to FDA	Submitted information on patients and Addendum to Schedule 10.
6/12/86	Letter to FDA	Submitted information on patients.
6/19/86	Letter to FDA	Submitted information on patients and clinical investigator.
7/8/86	Letter to FDA	Submitted information on patients.
7/9/86	Letter to FDA	Submitted information on patients.
7/11/86	Letter to FDA	Submitted information on patients and addendum to schedule 9.
7/24/86	Letter to FDA	Submitted information on patients and clinical investigators.

8/1/86	Letter to FDA	Submitted information on patients.
8/11/86	Letter to FDA	Submitted information on patients and clinical investigator.
8/20/86	Letter to FDA	Submitted information on patients and clinical investigators.
8/25/86	Letter to FDA	Submitted information on patients.
9/2/86	Letter to FDA	Submitted information on patients.
9/8/86	Letter to FDA	Submitted information on patients.
9/10/86	Letter to FDA	Submitted Annual Progress Report in three volumes.

9/12/86	Letter to FDA	Submitted information on patients and clinical investigators.
9/24/86	Letter to FDA	Submitted information on patients and clinical investigators.
10/2/86	Letter to FDA	Submitted information on patients and clinical investigators.
10/9/86	Letter to FDA	Submitted information on patients and clinical investigators.
10/13/86	Letter to FDA	Submitted information on patients.
10/16/86	Letter to FDA	Submitted information on patients and clinical investigator.
10/28/86	Letter to FDA	Submitted information on patients.

APPLICATION PHASE

12/6/84	HLR Memo	Telephoned Anti-Infective Division to verify desk review copies of NDA needed by FDA.
12/20/84	Letter to FDA	Submitted NDA for etretinate in 346 Volumes.
12/24/84	Letter from FDA	Acknowledged receipt of Roche's 12/20/84 NDA submission and assigned NDA # 19-369.
1/10/85	HLR Memo	FDA requested "Methods Validation Package."
1/31/85	Letter to FDA	Submitted Methods validation package for etretinate.

2/12/85	HLR Memo	FDA telephoned on 2/8/85 to supply names and addresses of two laboratories to which samples should be sent and requested a sample of etretinate.
2/19/85	HLR Memo	Roche telephoned two laboratories specified by FDA who will evaluate Roche's analytical methods to advise them of planned shipment of material.
2/27/85	HLR Memo	Shipped test materials and supplemental analytical information to two FDA test laboratories in Brooklyn, NY (hereinafter the "Brooklyn Lab") and Winchester, MA (hereinafter the "Winchester Lab").
2/28/85	HLR Memo	Telephoned FDA to discuss organization of NDA with reviewing medical officer.

3/1/85	Letter to FDA	Submitted additional technical information.
4/16/85	HLR Memo	Discussed case reports with FDA.
4/22/85	HLR Memo	Discussed Winchester Lab activities with FDA.
5/14/85	HLR Memo	Discussed upcoming meeting of Advisory Committee with FDA.
5/17/85	HLR Memo	Discussed upcoming meeting of Advisory Committee with FDA.
5/21/85	HLR Memo	FDA requested information on carcinogenicity study in mice.
5/22/85	HLR Memo	Telephoned FDA to respond to their 5/21/85 request.
5/23/85	HLR Memo	FDA requested further information of carcinogenicity study in mice.

5/28/85	HLR Memo	FDA requested additional information on safety.
5/29/85	Letter to FDA	Responded to FDA's 5/23/85 request
6/3/85	Letter to FDA	Submitted information to FDA for meeting with Advisory Committee.
6/5/85	Letter to FDA	Responded further to FDA's 5/23/85 request.
6/17/85	HLR Memo	Received information from FDA for upcoming Dermatologic Drugs Advisory Committee Meeting
6/24/85	HLR Memo	Met with Dermatologic Drugs Advisory Committee at FDA.
7/2/85	HLR Memo	Telephoned FDA to follow up on FDA's review of Roche's manufacturing and control data.

7/11/85	Letter to FDA	Revised Tegison® package insert.
7/19/85	Letter to FDA	Submitted revised draft package insert in response to FDA's 7/19/85 telephone request.
7/26/85	Letter to FDA	Submitted Amendment to Original NDA
7/26/85	HLR Memo	Confirmed 7/24/85 telephone conference with FDA regarding Draft Manufacturing and Control Comments
8/7/85	HLR Memo	Conducted a conference call with FDA regarding Draft Manufacturing and Control Comments.
8/7/85	Letter form FDA	Extended NDA review clock for 90 days.

8/15/85	HLR Memo	Followed up with FDA on conference call regarding Draft Manufacturing Control Comments.
8/16/85	HLR Letter	Responded to FDA's Draft Manufacturing and Control Comments.
8/16/85	Letter to FDA	Submitted safety update.
8/19/85	HLR Memo	Telephoned FDA to discuss Tegison Safety Update and Summary Basis of Approval.
9/3/85	Letter to FDA	Submitted draft sponsor - prepared Summary Basis of Approval.
9/4/85	Letter to FDA	Responded further to FDA's Draft Manufacturing and Control comments along with container labels and revised schedules and supporting data for new Tegision trade dress.

9/9/85	HLR Memo	Discussed Tegison® labelling with FDA.
9/12/85	HLR Memo	Delivered Draft Summary Basis of Approval for Tegison® and discussed remaining technical questions with NDA.
9/16/85	HLR Memo	Confirmed 9/12/85 telephone conference with FDA regarding Tegison® labelling.
10/1/85	HLR Memo	Telephoned FDA to update status of approvable letter and to discuss problems encountered by validation laboratories.
10/7/85	Letter to FDA	Confirmed 9/18/85 conference call with FDA regarding validation of analytical methods for Tegison®.
10/8/85	HLR Memo	Confirmed 10/4/85 telephone call from FDA requesting impurity samples.

10/21/85	HLR Memo	Confirmed 10/16/85 telephone call to FDA to discuss results of Brooklyn Lab validation.
10/28/85	HLR Memo	Consulted with FDA regarding indications section of Tegison® package insert.
10/28/85	HLR Memo	Telephone conversation with FDA regarding Brooklyn Lab's activities and Tegison® package insert
11/7/85	HLR Memo	Telephone FDA to update status of approvable letter for Tegison® and discussed validation.
11/14/85	Letter to FDA	Modified indications and usage section of the Tegison® package insert.

11/18/85	HLR Memo	Confirmed 11/12/85 meeting with FDA to discuss Brooklyn Lab validation results.
12/4/85	HLR Memo	Telephoned FDA to update status of approvable letter.
12/10/85	HLR Memo	Telephoned FDA to update status of approvable letter.
12/23/85	HLR Memo	Telephoned FDA on 12/16/85, 12/19/85 and 12/20/85 to update status of approvable letter.
1/3/86	HLR Memo	Telephoned FDA on 12/23/85, 12/24/85, 12/26/85, 12/30/85, 12/31/85 and 1/3/86 to update status of approvable letter.
1/27/86	HLR Memo	Met with FDA on 1/23/86 to discuss approvable letter.

2/10/86	HLR Memo	Telephoned FDA on 1/31/86, 2/3/86 and 2/7/86 to discuss status of approvable letter.
2/19/86	HLR Memo	Telephoned FDA to update status of approvable letter.
2/20/86	HLR Memo	Telephoned FDA on 2/19/86 to reply to FDA inquiry.
3/3/86	HLR Memo	Numerous telephone calls were made to FDA during week of 2/23/86 to update status of approvable letter.
3/18/86	HLR Memo	Met with FDA on 3/17/86 to discuss approvable letter.
3/19/86	Letter to FDA	Explained error in sample labeling
4/7/86	HLR Memo	Contacted FDA on 3/25/86, 3/31/86 and 4/3/86 regarding approvable letter.

5/13/86	HLR Memo	Eight (8) telephone calls were made to FDA between 4/18/86 and 5/12/86 to discuss approvable letter.
6/2/86	HLR Memo	Met with FDA on 5/23/86 to discuss approvable letter. FDA requested additional information. This information was supplied to FDA on 5/28/86. Telephone call to FDA on 5/30/86 to follow up on status of approvable letter.
6/19/86	HLR Memo	Numerous telephone calls to FDA between 6/2/86 and 6/17/86 to discuss approvable letter.

7/15/86	HLR Memo	Telephoned FDA on 6/26/86 and met with FDA on 7/2/86 to discuss approvable letter. Subsequent telephone calls were made to FDA on 7/3/86, 7/8/86, 7/9/86, and 7/10/86 to discuss approvable letter.
7/31/86	Letter from FDA	FDA sends Roche an Approvable Letter for Tegison ® stating that FDA has completed its review of the NDA but requesting additional information.
8/4/86	HLR Memo	Met with FDA on August 1, 1986 to discuss additional information requested by FDA in its 7/31/86 Approvable Letter and set up meeting for August 5, 1986 to discuss the timetable for submitting the requested information to FDA.

8/5/86	Letter to FDA	Confirmed that Roche would comply with the FDA's request for additional information.
9/10/86	HLR Memo	Discussed package insert for Tegison® with FDA in a September 8, 1986 telephone conversation.
9/10/86	Letter to FDA	Submitted Revised Package Insert for Tegison® to FDA.
9/22/86	HLR Memo	Numerous telephone calls were made to the FDA between September 16 and September 22 to discuss changes to the Tegison® package insert and to confirm other information requested by FDA.
9/25/86	Letter to FDA	Submitted Safety Update for 652 patients.

9/25/86	Letters to FDA	Submitted final printed labelling for package insert, container labelling, answers to specific FDA questions in Approvable Letter and Safety Update.
9/26/86	HLR Memo	Discussed Tegison® safety with FDA.
9/30/86	Letter form FDA	FDA approves Tegison® for commercial marketing or use under section 505 of the FD&C.

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